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SWEAT SECRETION IN MAN*

VI. SPINAL REFLEX SWEATING

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During World War I Head and Riddoch[1] observed outbreaks of drenching perspiration in soldiers with severe transverse lesions of the spinal cord. They found that this type of sweating response was not thermoregulatory and that it was localized to parts of the body which received their nerve supply from segments of the spinal cord below the transverse lesion. The authors correlated the various vegetative disturbances observed with transverse lesions of the spinal cord, such as abnormal sweating and disturbance of vesical and genital functions, with the pathologic alterations in somatic functions. They pointed out that the abnormal sweating response is, like all the other changes, a manifestation of the spinal mass reflex. The observations of Head and Riddoch were confirmed and extended by Thomas,[2] who emphasized the analogy between the disturbances of sweating and those of piloerection in spinal man. Since then there have been no new contributions on the subject. The following observations made in 3 cases at the University of Michigan Hospital may serve to illustrate the salient points of the problem and, at the same time, to suggest therapeutic measures.

CLINICAL OBSERVATIONS

CASE 1.—*Almost complete transverse lesion of the cord at the fifth and sixth cervical segments. Total absence of thermoregulatory sweating. Spinal sweating of the upper half of the body, which was abolished by sympathectomy.*

History.—On June 11, 1938 M. E. C., a man aged 20, broke his neck while diving into shallow water. Immediate motor and sensory paralysis below the neck resulted. A decompressive laminectomy was done elsewhere. The patient was admitted on Nov. 11, 1942 with the following complaints: involuntary jerking of the paralyzed legs; frequent involuntary evacuation of the bladder, and attacks of excessive sweating, mainly on the left side of the face, neck and upper part of the chest and the left upper extremity. The sweating was induced by distention of, or pressure on, the bladder, by his sitting in the upright position and by any stimulus producing reflex movements of the legs.

Examination.—There was evidence of an old fracture dislocation of the fifth and sixth cervical vertebrae.

Neurologic examination indicated interruption of the long pathways of the spinal cord at the level of the fifth cervical segment, viz., volitional paralysis of muscles of the distal parts of the upper extremities, the trunk, the lower extremities and the bladder and rectum. All forms of sensation were diminished below the fourth cervical segment and were abolished below the seventh cervical segment.

There was evidence of destruction of the fifth and sixth segments of the cord, namely, atrophic paralysis of the muscles supplied by these segments, with loss of corresponding reflexes (biceps and radius reflexes).

There was evidence of autonomous activity of the spinal cord below the level of the transverse lesion, viz., spasticity of muscles of the trunk and of the lower extremities, with exaggeration of the deep reflexes; spinal flexor reflex synergias could be elicited below the midthoracic level, and the Babinski sign was present bilaterally. The vesical disturbances were characteristic of the uninhibited spastic reflex bladder.

Sweating Responses.—To ascertain the state of the descending supraspinal sympathetic pathways, a thermoregulatory sweating test was performed. It showed total anhidrosis of the entire body (fig. 2), proof that the spinal sweating centers were completely isolated from their supraspinal connections. The presence of a Horner syndrome on the left side indicated that the supraspinal oculopupillary path was also interrupted on that side.

When the patient sat erect for fifteen minutes, he began to sweat profusely, first over the left side of the forehead and then over the left side of the neck and upper part of the chest and the left arm; later, sweating, with the same distribution, appeared on the right side, although to a less pronounced degree (figs. 1 *A* and 2). In association with the sweating, a pilomotor reaction occurred over the entire left upper extremity.

The spinal sweating response could be evoked easily by distention of the bladder, by external pressure on the suprapubic region and by the patient's assuming the sitting posture. Less profuse sweating could be obtained by repeated elicitation of spinal defense reflexes (pinprick applied to the soles of the feet or passive plantar flexion of the feet and toes).

To study the role of visceral afferent paths in the production of spinal sweating, a regional block of the splanchnic nerves was performed. Paravertebral injec-

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*List, C. F., and Peet, M. M.: Sweat Secretion in Man: I. Sweating Responses in Normal Persons, Arch. Neurol. & Psychiat., **39**:1228-1237 (June) 1938.

1. Head, H., and Riddoch, G.: The Automatic Bladder, Excessive Sweating and Some Other Reflex Conditions, in Gross Injuries of the Spinal Cord, Brain **40**:188-263, 1917.

2. Thomas, A.: Le réflexe pilomoteur. Étude anatomo-clinique sur le système sympathique, Paris, Masson & Cie, 1921.

tions of a 1 per cent solution of procaine hydrochloride were made into the tenth, eleventh and twelfth intercostal spaces bilaterally, 10 cc. being used for each of the six areas of injection. The blood pressure (95 systolic and 50 diastolic) when the patient was in the sitting position did not change after the injection. There were no other constitutional changes. The usual postural sweating response failed to appear after the paravertebral injection. Only minimal perspiration occurred over the left side of the face, neck and shoulder and the left upper extremity, after a long period of waiting and after frequent elicitation of the mass reflex of the legs and continuous suprapubic pressure.

Fig. 1.—*A*, *B* and *C* (case 1), spinal reflex sweating in a case of a transverse lesion in the fifth and sixth cervical segments: *A*, before operation; *B*, nine months after removal of the stellate and the second thoracic sympathetic ganglion on the left side, and, *C*, after additional removal of the stellate and the second thoracic ganglion on the right side. *D* (case 2), simultaneous thermoregulatory and spinal reflex sweating in a case of a transverse lesion in the third and fourth dorsal segments.

Operation and Subsequent Observations.—On Nov. 17, 1942 the stellate and second thoracic sympathetic ganglia on the left side were removed through the posterior approach by one of us (C. F. L.).

A spinal sweating test was performed twelve days after operation. The entire left side of the face, neck and upper part of the chest and the left upper extremity remained anhidrotic; however, slight sweating occurred in a bandlike area extending from the third rib to the nipple line, on the left side. Slight perspiration also appeared on the right side of the forehead and neck. The Horner syndrome on the left side had become more pronounced after the operation.

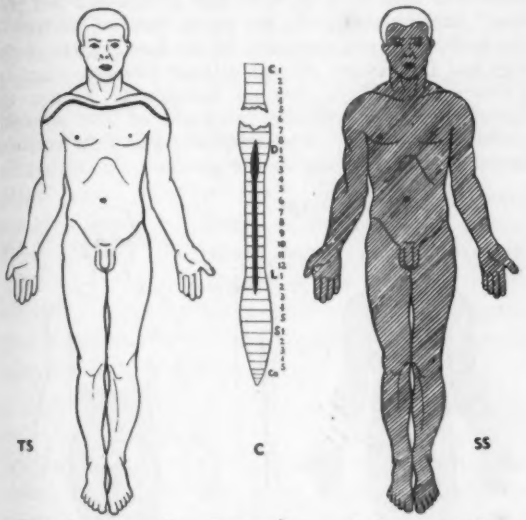

Fig. 2 (case 1).—Comparison of thermoregulatory and spinal sweating responses in a case of a transverse lesion in the fifth and sixth cervical segments.

In this figure, and in figures 3 and 4, thermoregulatory sweating is schematically recorded on the left side (*TS*), and spinal sweating on the right side (*SS*). The sweating areas are shaded, without regard for quantitative differences. The black line in figure *TS* represents the sensory level. *C* is a schematic drawing of the spinal cord. The segments, the sympathetic cell column and the location of the transverse lesion are indicated.

The patient was readmitted on Aug. 13, 1943 with the complaint that the right side now perspired almost as profusely as did the left side before the operation. The left side had remained dry except in the midthoracic region. Examination showed no change in the neurologic status.

With the patient sitting upright, suprapubic pressure was exerted and the mass reflex of the legs repeatedly elicited. Strong sweating occurred on the right side of the face, neck and upper part of the chest and the right upper extremity. On the left side the previously sympathectomized area remained dry. Below this denervated area, however, there was a zone of circumscribed hyperhidrosis, extending from the axilla to the skin covering the third to the fifth rib. Sweating was equally distributed on the two sides below the nipple line (fig. 1 *B*).

Since the patient was anxious to have the sweating of the right side abolished, the stellate and second dorsal sympathetic ganglia on the right side were removed through the posterior approach on Aug. 18, 1943, by one of us (C. F. L.).

Two weeks after the second operation the spinal sweating test revealed total anhidrosis of the head, neck and upper part of the chest and of both upper extremities, but sweating persisted in the axillas and on the thoracic wall below the third ribs (fig. 1 *C*). There was also a bilateral Horner syndrome.

The patient decided to have further sympathectomies, either by operation or by paravertebral injection of alcohol, if the residual sweating of the trunk became bothersome in the future.

CASE 2.—*Total transverse lesion of the spinal cord at the level of the third and fourth dorsal segments. Preservation of thermoregulatory sweating of the head and neck only. Spinal reflex sweating of the trunk and inner aspects of the arms, which was abolished by multiple paravertebral injections of alcohol.*

History.—H. F., a woman aged 21, fractured her spine on May 21, 1941, with immediate motor and sensory paralysis below the axillas. A decompressive laminectomy was performed elsewhere.

She was admitted to the University of Michigan Hospital on March 16, 1943 for the treatment of multiple bed sores, severe infection of the urinary tract and excessive sweating of the trunk. The sweating was elicited when she sat upright or was in the recumbent lateral position (right or left side). She stated that occasionally there was mild sweating of the upper extremities as well, but that exposure to heat produced sweating only of the face and neck.

Examinations.—There was an old compression fracture of the third and fourth thoracic vertebrae, with associated kyphosis and a residual bony defect from laminectomy. Neurologic examination proved that conduction of nerve impulses in the spinal cord was totally interrupted at the level of the fourth thoracic

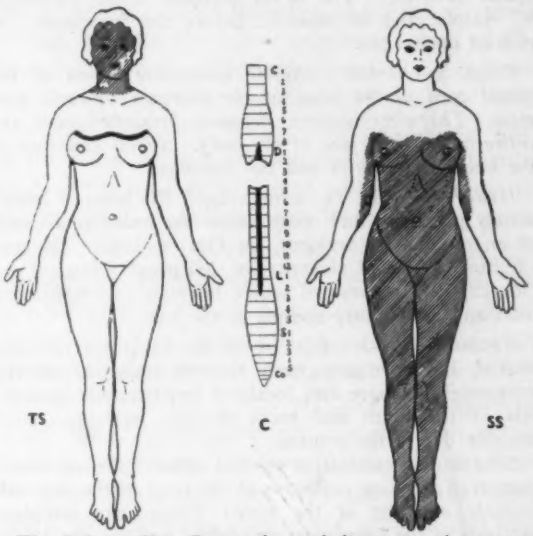

Fig. 3 (case 2).—Comparison of thermoregulatory and spinal sweating in a case of a transverse lesion in the third and fourth dorsal segments.

segment: There was complete volitional paralysis of all muscles below the third intercostal space. All forms of sensation were abolished below the level of the fourth thoracic segment.

There was evidence of autonomous activity of the spinal cord below the transverse lesion: The lower extremities exhibited moderate spasticity and considerable exaggeration of deep reflexes. Mild flexor

synergias of the lower extremity and the Babinski sign could be elicited bilaterally. The vesical disturbances were characteristic of the uninhibited spastic reflex bladder.

Sweating Responses.—The thermoregulatory sweating test showed abundant sweating of the face and moderate sweating of the neck (fig. 3). Anhidrosis below this level proved that only the sympathetic cells of the first and second thoracic segments had retained their normal supraspinal connections, but that the descending sympathetic path was interrupted below that level.

Profuse sweating of the trunk was observed, especially on the left side, as well as considerable sweating of the lower extremity on one occasion, when the patient was lying on her left side. On another occasion the patient sat up in a chair for half an hour. This posture, and repeated elicitation of the flexor defense reflex of the lower extremity bilaterally, evoked profuse sweating in the axillas, on the inner aspects of the arms and on the trunk below the third ribs (especially on the left side). Simultaneous thermoregulatory sweating occurred on the face and neck, since this observation was made on a warm summer day (figs. 1 *D* and 3).

A series of paravertebral injections of 50 per cent alcohol (3 cc. each) was given in order to abolish the annoying spinal sweating. At the first session injections were made into the fourth to the ninth intercostal space on the left side. At a second stage injections were made into the second to the fourth intercostal space bilaterally (with the patient under anesthesia induced with sodium pentothal, since these spaces were partially above the level of analgesia). At a third session injections were made into the fifth to the tenth intercostal space on the right side. The result was complete abolition of spinal sweating. The blood pressure, which measured 98 systolic and 80 diastolic before the injections, remained unchanged.

CASE 3.—*Almost complete transverse lesion of the spinal cord at the level of the eleventh thoracic segment. Thermoregulatory sweating preserved over the entire anterior surface of the body. Spinal sweating of the lower extremities and the abdomen.*

History.—A. E. D., a man aged 28, became immediately paralyzed and numb below the waist as a result of an automobile accident, on Oct. 8, 1942. He was admitted to the University of Michigan Hospital on Oct. 22, 1943 because of severe infection of the urinary tract and involuntary spasms of the legs.

Examination.—No fracture of the spine was demonstrated, but roentgenograms showed reduction of the intervertebral space and localized hypertrophic spondylitis of the ninth and tenth thoracic vertebrae, presumably due to the trauma.

Neurologic examination showed almost complete interruption of the long pathways at the level of the eleventh thoracic segment of the cord: There was complete paralysis of the lowermost abdominal muscles, the lower extremities, the bladder and the rectum. On the left side all forms of sensation were completely abolished below the eleventh thoracic dermatome; on the right side, however, the superficial forms of sensation were still partially preserved, whereas vibratory and position senses were lost.

There was striking evidence of autonomous activity of the spinal cord below the level of the lesion: Both legs were extremely spastic, the right being in extension and the left in flexion, with exaggeration of the deep reflexes. Flexor reflex synergias (and rarely extensor synergias as well) of the lower extremity and the Babinski sign could be elicited bilaterally by slight exteroceptive and proprioceptive stimulation below the groin. The bladder was of small capacity and of spastic reflex type, with partial retention of sensation.

Sweating and Pilomotor Responses.—A thermoregulatory sweating test was done with the patient in the recumbent supine position in order to determine the condition of the central sympathetic pathway. Special care was taken to have the legs completely relaxed and to avoid all stimuli which might evoke reflex contractions of the legs. There was no spontaneous sweating of the legs or abdomen at the beginning of the test. Thermoregulatory sweating began in the lower abdominal region; later, it became generalized and profuse, covering uniformly the entire anterior surface of the body, with the exception of the lower parts of the legs and feet, which showed delayed sweating (fig. 4). Unfortunately, there was no opportunity to test the thermoregulatory sweating response of the posterior surface of the body. The encephalic pilomotor response extended as far down as the groins.

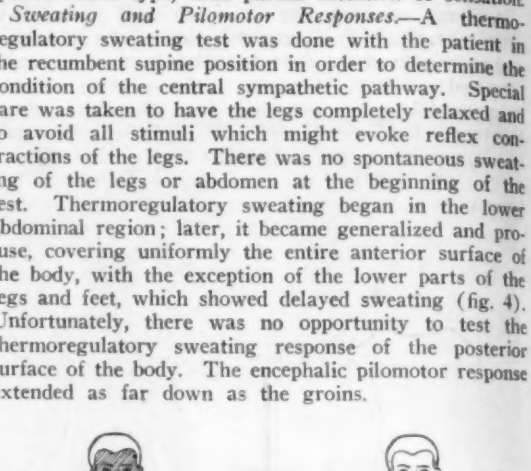

Fig. 4 (case 3).—Comparison of thermoregulatory and spinal sweating in a case of a transverse lesion in the eleventh dorsal segment.

Unless special precautions were taken, slight spontaneous sweating occurred on both legs, particularly the left one, and over the lower abdominal region when the patient was in the recumbent supine position. This sweating appeared to be associated with, or induced by, the frequent spontaneous reflex movements of the legs; in fact, sustained and repetitive exteroceptive and proprioceptive stimulation of the lower extremities greatly increased the sweating, which then extended almost up to the costal arches (fig. 4). At the same time, the stimulation evoked occasional waves of piloerection on the lower part of the abdomen and on both thighs.

COMMENT

Although the actual extent of the lesion in the cord was not anatomically verified in our 3 cases, from a functional standpoint the cord had been totally, or at least almost completely, transected. The neurologic examination proved that conduction of both efferent and afferent somatic impulses was blocked by the transverse

lesion, and the thermoregulatory sweating test showed that the spinal paths of visceral efferent fibers, such as the sweat fibers, were interrupted as well. Consequently, the sweating observed below the level of the lesion must depend on activities of the (functionally) severed distal portion of the spinal cord. In fact, spinal sweating is observed only when neural conduction in the cord is either severely damaged or totally interrupted. It is a release phenomenon which presupposes the liberation of intact spinal centers from the inhibitory influence of supraspinal levels and corresponds to other manifestations of spinal automatism. The constancy of the spinal sweating response, its short latent period after certain types of stimulation, its characteristic distribution and, finally, its association with other responses of the somatic and visceral spheres leave no doubt as to its reflex nature. One should, therefore, be able to define the afferent and efferent arcs of the sweating reflex, elicit the response by certain types of stimulation and abolish it by interruption of its specific afferent or efferent pathway.

Afferent Pathway.—Spinal sweating is elicited only by stimuli which act on parts of the body possessing afferent connections with the severed distal portion of the spinal cord. The afferent stimuli capable of evoking the spinal sweating reflex may be classified as visceral proprioceptive, visceral nociceptive, somatic proprioceptive and somatic nociceptive.

Visceral proprioceptive stimuli appear to be particularly effective: For instance, spontaneous distention of the bladder by urine and artificial distention by irrigation or external pressure on the suprapubic region (Credé's maneuver) easily evoke spinal sweating. Distention of the bowel seems to have a similar, though less striking, effect. The outbreaks of sweating when the subject is in certain postures (cases 1 and 2) may be explained by the assumption that postural changes of the viscera may stimulate proprioceptors in suspending and supporting structures, such as the mesenterium, the omentum and the peritoneal ligaments.

On the other hand, nociceptive visceral stimuli may bring on the sweating, e. g., irritation of pain or thermic receptors in the bladder by catheterization and other intravesical surgical procedures or by inflammatory processes.

Realizing the important role played by the visceral afferent impulses, we tried to interrupt the visceral afferent path by bilateral paravertebral block of the splanchnic nerves with procaine (case 1). Actually, this procedure all but abolished the sweating response to the application of usually effective stimuli.

Stimulation of somatic sensory receptors may also elicit spinal sweating, but the response is not as constant and vigorous as that obtained by visceral stimulation. Proprioceptive stimuli, such as passive plantar flexion of the foot and toes (the so-called Marie-Foix maneuver), and exteroceptive (nociceptive) stimuli, such as pin prick or thermic agents, may be equally effective.

Occasionally, subliminal physiologic stimuli appear to set up a constant excitatory state in the autonomous stump of the cord, with resulting mild spontaneous hyperhidrosis of the corresponding parts of the body (case 3).

It should be noted that the spinal sweating response may vary considerably in intensity in the same person, when the examination is repeated under apparently identical conditions.

Efferent Pathway.—The efferent limb of the spinal sweating reflex mechanism begins in cells of the intermediolateral column; the axons of these cells pass as preganglionic fibers via the anterior roots and the white rami communicantes to the ganglia of the sympathetic chain; here a synapse occurs, and then the peripheral sympathetic neurons pass as postganglionic fibers via the gray rami communicantes and the peripheral nerves to the sweat glands.

Since the spinal sweating reflex is mediated exclusively by the distal stump of the spinal cord, the upper border of the area of spinal sweating should indicate the lower segmental level of the transverse lesion. The lower level of the thermoregulatory sweating response, on the other hand, which is mediated by the intact proximal part of the cord, should indicate the upper segmental level of the transverse lesion. In case 2 (fig. 3), for instance, spinal sweating extended up to the axillas and the inner surfaces of the arms; the sweat fibers transmitting this response carry the sympathetic impulses from the fifth thoracic segment. The distal border of the area of thermoregulatory sweating was at the lower part of the neck, which receives its segmental sympathetic innervation from the first and second thoracic segments. In case 3 (fig. 4) the level of spinal sweating extended nearly to the costal arch, an indication that some sympathetic cells of the eleventh thoracic segment were spared by the lesion and responded to reflex stimulation. The thermoregulatory sweating extended distally to the anterior surfaces of the lower portions of the legs and feet. According to Foerster,[3] these parts receive their sympathetic innervation from

3. Foerster, O.: Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, pp. 1-403.

as high a level as the tenth thoracic segment, i. e., the segment immediately above the transverse lesion.

If, therefore, the level of a transverse lesion is known, the lower level of thermoregulatory sweating and the upper level of spinal sweating may be used to study the spinal segmental sympathetic innervation of the skin. In this manner, Foerster [3] and Thomas [2] were able to establish a system of sympathetic dermatomes, based on numerous observations on transverse lesions. Our own series of cases is too small to justify further elaboration of the segmental system described by these authors. It is sufficient to mention a few important points: The spinal sympathetic dermatomes do not correspond to the well known sensory dermatomes; they are much larger. For this reason, the sweating level in cases of a transverse lesion of the cord is, as a rule, not identical with the sensory level. Foerster [3] observed that stimulation of the fifth anterior thoracic root, for instance, produced sweating in a wide area extending from the umbilical level to the axilla, and in some cases including even the entire arm on the same side. In contrast, the fifth sensory thoracic dermatome forms a narrow band confined to the mamillary area. Because of their large size, the sympathetic dermatomes overlap more than do the sensory dermatomes; consequently, the segmental borderline is less sharply defined for sweating than for sensation. Whether or not the level of thermoregulatory and that of spinal sweating are superimposed on each other depends on factors which are variable in each case, such as the length of the lesion in the cord and associated injury of the anterior nerve roots or of the ganglionated chain. In case 3 there was considerable overlapping of thermoregulatory and spinal sweating (fig. 4) because the small transverse lesion left parts of the tenth and eleventh segments still functionally intact. Similarly, in an observation by Foerster, in a case of a transverse lesion in the eighth dorsal segment, the areas of thermoregulatory and of spinal sweating were superimposed on each other (fig. 5). The extensive lesion in case 2, on the other hand, abolished sympathetic functions from the lower portion of the second thoracic segment to the upper part of the fifth thoracic segment, an effect accounting for the anhidrotic zone between the level of thermoregulatory sweating and the level of spinal sweating (fig. 3).

Unless conditions of observation are strictly controlled, thermoregulatory sweating and spinal sweating may occur simultaneously (cases 2 and 3). One may then gain the erroneous impression that the sweating response is normal, because it is universal and without level. Such a situation may arise in the presence of urosepsis with distention of the bladder: The fever caused by pyelocystitis may evoke a thermoregulatory sweating response, while distention of the bladder may be responsible for the simultaneous outbreak of spinal sweating.

It is worthy of mention that spinal reflex sweating often is most active near its upper level, i. e., in an area which obtains its sympathetic innervation from spinal segments immediately below the transverse lesion. This was noted by Head and Riddoch [1] and Thomas [2] and was observed in our cases. It is a common observation in cases of disturbed sweat secretion

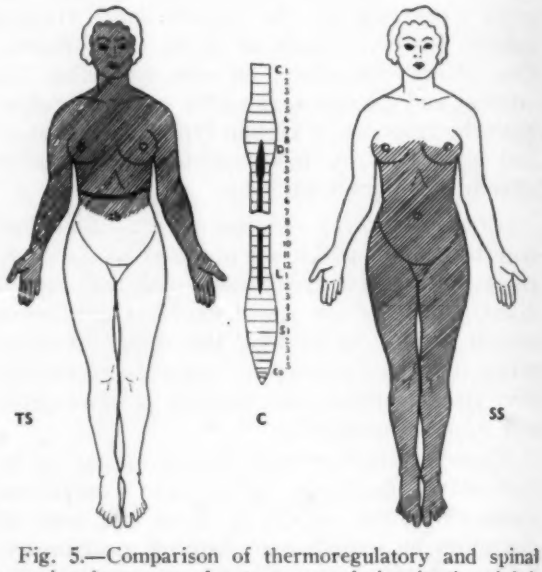

Fig. 5.—Comparison of thermoregulatory and spinal sweating in a case of a transverse lesion in the eighth dorsal segment (after Foerster).

that the activity of the sweat glands is increased in the area surrounding the anhidrotic region (so-called borderline, or perilesionary, sweating).

Spinal sweating is not an isolated phenomenon but is always associated with other manifestations of spinal reflex activity, such as piloerection, evacuation of the bladder and spinal defense movements. Outbreaks of spinal sweating appear to be more closely coordinated with other visceral responses, especially with piloerection, than with somatic motor responses. Even though flexor and extensor reflex synergias are the most frequent and characteristic signs of spinal automatism, such reflex movements are not often accompanied by sweating; in fact, spinal defense reflexes may be present when the spinal sweating response cannot yet be elicited, and, conversely, the spinal sweating response

disappears toward the end of life, before the spinal defense reflex is abolished (Thomas [2]).

Treatment of Spinal Sweating.—Spinal sweating may be so excessive that it greatly annoys the patient or is even his outstanding complaint. The patients described in cases 1 and 2, for example, were resigned to the paralysis, automatic bladder and defense movements, but they asked relief from the attacks of drenching perspiration, which were extremely embarrassing and necessitated frequent change of clothing. Theoretically, blocking of the afferent pathways should diminish, or even arrest, spinal sweating, but this approach is impractical, since it is difficult, if not impossible, to block all afferent impulses. Sweating can be effectively stopped, however, by interruption of its efferent pathway, the sympathetic chain. Sympathetic ganglionectomy produces regional anhidrosis of the cutaneous area supplied by the resected ganglion. For the relief of hyperhidrosis, sympathectomy may be either preganglionic or postganglionic; this is in contrast to the surgical treatment of vasospastic conditions.

If the hyperhidrosis involves the head, neck and upper extremities (as in case 1), removal of the stellate and second thoracic ganglia will interrupt the cervicothoracic outflow.

If the trunk is perspiring excessively, extensive dorsal sympathectomy is required. This operation involves too much shock for use with weakened patients. Section of intercostal nerves should accomplish the same result with lesser risk, and the procedure is not objectionable if sensory and motor paralyses are already present. Sympathetic denervation by multiple paravertebral injections of alcohol, however, appears to be the best procedure in cases of spinal hyperhidrosis involving the trunk (case 2). The anesthesia due to the transverse lesion prevents pain from intercostal neuritis after the injection. One might theoretically expect a lowering of blood pressure after extensive dorsal sympathectomy (surgical or by injection), as a result of the interruption of the splanchnic nerves; yet the blood pressure remains unchanged because the supraspinal vasoconstrictor pathway is already severed by the transverse lesion.

In treatment of spinal hyperhidrosis of the lower extremities, which we had no occasion to undertake, lumbar ganglionectomy (first to fourth lumbar) should be satisfactory.

SUMMARY

Spinal reflex sweating is a pathologic type of sweating observed with severe or complete transverse lesions of the cord.

It is a release phenomenon and a component of the spinal mass reflex; hence it may be induced by any afferent stimulus acting on the distal portion of the cord. Its efferent mechanism is also mediated by the distal stump of the cord and peripherally by the thoracolumbar portion of the sympathetic system.

If the site of a transverse lesion is known, the lower level of thermoregulatory sweating and the upper level of spinal sweating may be used to study the spinal segmental innervation of sweat glands. The dermatomes for sweating are much larger than the corresponding sensory dermatomes.

Spinal sweating tends to be greatest near its proximal borderline.

Relief from excessive spinal sweating can be obtained by sympathectomy.

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EFFECTS OF VARIATIONS IN INTRACRANIAL PRESSURE

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CHICAGO

I. EFFECT OF RAISED INTRACRANIAL PRESSURE ON CONSCIOUSNESS

The experiments here reported were begun with the intention of studying the effect of experimentally produced cerebral edema on consciousness in the dog. To do this, distilled water was perfused into the anatomic central end of the common carotid artery, and observations were made on whether or not this procedure would render the animal comatose. Kymographic records were simultaneously taken of the respiration, the general carotid blood pressure, the cerebrospinal fluid pressure in the cisterna magna and the pressure in the brain tissue (intracerebral pressure). It was at first assumed that the pressure in the lateral ventricles was being accurately recorded by measurement of the cisternal pressure. The fallacy of this assumption was later demonstrated by some chance measurements of the intraventricular pressure. In subsequent experiments the intraventricular pressure was simultaneously recorded with a mercury manometer.

METHODS

Ether was the anesthetic employed in all the experiments to be reported. For the recording of intracerebral pressure (pressure in the brain tissue) a method similar to that employed by Kerr and Scott[1] for measuring pressure in muscle tissue was utilized. To the upper arm of a mercury manometer a 4 inch (10 cm.) length of small bore glass tubing is attached by means of rubber tubing. To the end of the glass tubing, by means of an adapter, is fastened a 22 gage needle the tip of which has been plugged with solder and in the sides of which, near the tip, small holes have been drilled. The pressure in this system can be raised by means of a sphygmomanometer bulb attached to the lower arm of the mercury manometer. The plugged tip and the holes drilled in the sides of the needle are a necessary precaution to prevent plugging of the lumen as the needle is inserted through the dura into the soft brain tissue. Isotonic solution of three chlorides U. S. P. is forced through the lateral holes of the needle into the glass tubing so that a fluid meniscus now becomes visible in the tube. The needle is then inserted directly into the brain tissue through the intact dura mater. The operator then slowly raises the pressure on the fluid in the tube by squeezing the rubber bulb until the meniscus just begins to move toward the brain tissue. This level of pressure is recorded by the mercury manometer on the kymograph paper and is taken as the intracerebral pressure.

Aside from the applicability of the physical principle involved in this method of measurement of tissue pressure, two experimental observations corroborate its reliability: (*a*) As the cerebrospinal fluid pressure is raised (through the cisterna magna), the intracerebral pressure closely parallels the new levels of the cerebrospinal fluid pressure as measured in the lateral ventricles of the brain; (*b*) at any level to which the cerebrospinal fluid pressure and the intracerebral pressure may be raised, below the levels of the diastolic blood pressure, the meniscus in the measuring device is seen to pulsate as it moves toward the brain tissue while the intracerebral pressure is being measured. Since the pulsations of blood vessels in the brain tissue would impart to the tissue such a pulsation at all levels of tissue pressure less than arterial blood pressure, the fact that this pulsation is seen in the measuring device is indicative of the actual measurement of the tissue pressure.

Since there is a pressure wave, or pulse, in the brain tissue, a serious drawback of this method of tissue pressure measurement is its discontinuous nature. The pressure wave in the brain tissue may have both a respiratory and an arterial component, which will vary in magnitude under different conditions. Ordinarily this pulse appears small. Under some of the experimental conditions to be described the pulse appeared much increased in amplitude, and here an effort was made to take all pressure readings at the diastole of the pulse. The introduction of fluid into the brain tissue at the point of measurement must also alter to some degree the pressure of the tissue there. If care is exercised in raising the pressure on the meniscus to just the level at which the meniscus begins to pulsate, this method of tissue pressure measurement can be fairly accurate. The personal error in judging this point is estimated at ± 3 to ± 5 mm. of mercury.

Pressure in the lateral ventricle of the brain was measured with the same kind of device as that used in measurement of the intracerebral pressure. The pressure necessary to prevent the fluid in the ventricle from rushing up the needle into the glass tubing was taken as the level of intraventricular pressure. This method is extremely accurate, since little, if any, fluid is lost from the ventricle in making the measurement.

Pressure in the cisterna magna was measured by means of a mercury manometer connected with a 16 gage needle which had been shoved through the muscles of the neck and the occipitoatlantal ligament into the cisterna magna. Isotonic solution of three chlorides was used in this arrangement.

The blood pressure was recorded from the common carotid artery by means of a mercury manometer and respiration by the usual pneumograph-tambour technic.

For the purposes of this experiment the animal was regarded as unconscious when, after being allowed to exhale the volatile anesthetic, it lay quietly on the operating board and did not respond as a whole to ordinarily painful stimuli or to sound. Struggling and

From the Department of Physiology, University of Chicago.

1. Kerr, J. D. O., and Scott, L. D. W.: Brit. M. J. **2**:758, 1936.

return of ability of the animal to react as a whole to painful stimuli and to sound after being allowed to exhale the volatile anesthetic was considered an indication of return to consciousness.

OBSERVATIONS

SERIES 1 (12 experiments; 2 control experiments).—*Effect of water perfusion on intracranial pressure and consciousness in the dog.*

Procedure.—The animal was etherized, and anesthesia was continued by means of inhalations from an ether bottle attached to the tracheal cannula. Better results were obtained if the animal lay on its side with the head in a normal or a slightly flexed position rather than on its abdomen with the head extended. It was early recognized that less distilled water need be perfused for a given result with the animal in the former position. The common carotid artery was ligated on one side; the blood pressure was recorded from its anatomic peripheral end, and distilled water was perfused by hydrostatic pressure into its cannulated anatomic central end. The cisternal pressure in the cisterna magna and the intracerebral pressure were measured, as previously described. In 3 of the experiments no records of the cisternal pressure were obtained. In 5 of the experiments the intraventricular pressure was recorded, as previously described.

TABLE 1.—*Data on Water Perfusion Experiments on Twelve Animals*

Experiment No.	Weight of Animal, Kg.	Amount of Water Perfused per Kg., Cc.	Rate of Perfusion, Cc./Min.	Intracerebral Pressure When Animal Was Comatose, Mm. Hg	Intraventricular Pressure When Animal Was Comatose, Mm. Hg	Cisternal Pressure When Animal Was in Coma, Mm. Hg	Time Required to Reach Comatose State, Min.	Blood Pressure at Start of Experiment, Mm. Hg	Blood Pressure When Comatose State Was Reached, Mm. Hg	Diastolic Blood Pressure Minus Intracerebral Pressure When Coma Was Reached, Mm. Hg
1	13.5	111	14	72	No record	0	96	140/120	160/130	58
2	10	60	8	120	110	No record	70	134/120	170/160	40
3	11	136	12-16	120	No record	No record	112	165/154	180/168	48
4	8.5	165	10-14	100	No record	No record	150	170/160	168/146	46
5	6	250	16.5-10	80	No record	50	120	122/113	112/100	20
6	11	110	12-18	110	No record	60	87	162/150	170/128	18
7	11.2	87	7-8	90	No record	45	92	162/158	150/120	30
8	17.2	160	13.5	70	76	0	220	118/104	250/190	120
9	13.7	65	10	74	72	44	150	104/ 90	160/110	36
10	6.9	173	9	80	60	35	200	98/ 80	190/110	30
11	17.2	92.5	9	85	90	22	206	150/140	138/110	25
12	7.2	111	11	76	70	0	100	Variable	135/110	34

Results.—As distilled water was perfused into the animal, at the rate of approximately 10 cc. per minute, the intracerebral and intraventricular pressures began to rise, exceeding the cisternal pressure, which had also risen. The height to which the cisternal pressure rose varied with each experiment, as indicated in table 1. In 3 experiments the cisterna magna was allowed to be open to the exterior at variable intervals after the start of the experiment. This had no effect on the heights to which the intracerebral and the intraventricular pressure rose. As these pressures reached certain levels in the course of their ascent, the ether was removed. The commencement of struggling and other criteria previously mentioned were considered evidence of return to consciousness, in which event the anesthetic was again administered and the intracerebral and intraventricular pressures were allowed to reach higher levels. In most of the experiments it appeared evident that the return to consciousness and the readministration of the anesthetic hastened the rise of the intracerebral and the intraventricular pressure. After the intracerebral pressure had reached a level between 50 and 20 mm. of mercury below the diastolic blood pressure, as measured with the mercury manometer, the animal no longer exhibited ability to struggle after sufficient time had been allowed for it to blow off the anesthetic. (In experiment 1 the intracerebral pressure was 60 mm. of mercury below the diastolic blood pressure when coma was reached; in experiment 8 it was 120 mm. of mercury below.)

As a rule, if the animal did not begin to struggle within forty minutes after removal of the anesthetic, it remained comatose for the duration of the experiment. At these levels of the intracerebral pressure the fluctuations of the meniscus in the instruments for measurement of the intracerebral and intraventricular pressures were much larger than those at the beginning of the experiment, when low intracerebral and intraventricular pressures prevailed.

When the intracerebral pressure reached levels closer to the diastolic blood pressure, death resulted from circulatory and respiratory failure. Respiration became laborious and stertorous; the heart rate was very slow, and vagal beats might develop. Terminally one of two things happened: (*a*) The blood pressure might rise to high levels, over 200 systolic, and then descend rapidly to zero as the respiration first became embarrassed and then stopped. Such a terminal rise occurred in one-half the water perfusion experiments. (*b*) Vagal heart beats might become more prominent and blood pressure and

respiration fail without appearance of the terminal hypertension described in *a*. The intracerebral and the intraventricular pressure at this terminal stage paralleled the blood pressure in its rise and fall. Figure 1, the record from a typical experiment, and the following protocol of such an experiment demonstrate this point.

Dog 10 (Sept. 10, 1942): Ether anesthesia; weight, 6.9 Kg.

Time (P. M.)	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg	Blood Pressure	Comment
1:00	6	0	Slightly negative	96/ 80	
1:05	12	6	15	.....	Perfusion of water at rate of 9 cc. per min. begun
1:30	14	8	15	124/ 98	
	14	18	16		
2:00	14	28	22	134/108	Perfusion of 500 cc. of water here
	14	34	35		
2:28	14	36	39	164/130	Ether removed here
	15	42	47		
2:50	..	..	..	.....	Ether increased as animal struggled
3:02	18	49	55	178/130	Perfusion of 1,000 cc. of water to this point
	24	50	69		
3:25	25	56	68	176/134	Ether removed here
3:40	27	60	70	176/134	Ether increased, as animal struggled
3:50	28	63	80	.....	Ether removed
4:00	28	66	79	194/134	Animal shivering
4:12	32	70	90	186/128	Water off 1,200 cc. to this point
4:16	34	64	87	180/136	Large pulsations noted in intraventricular and intracerebral pressure measuring needles
4:24	35	60	79	190/110	Extension in forelimbs, and respiration, which heretofore had been more or less normal, became labored
4:27	0	..	..	.....	Cisterna magna opened to exterior
4:30	0	80	97	180/110	Animal lying quietly 40 min. after ether removed
4:37	0	108	124	180/140	Blood pressure rising rapidly
4:40	0	128	154	232/172	
4:45	0	..	50	80/ 66	Respiration became difficult and stopped; animal dying
4:48	0	14	14	14	Death

When the animal was in a comatose state, it lay on the operating board with a certain amount of increased muscular tenseness and might shiver somewhat. Rigidity was sometimes present in the forelimbs or hindlimbs or both. Ocular and flexion reflexes were active. Respiration was stertorous. Defecation, urination and vomiting sometimes occurred. Attention is also called to the slow pulse, the prominent blood pressure and the increase in amplitude of the intracerebral and intraventricular pulsations at these high pressure levels.

Experiments of this type were performed on 12 animals. The pertinent data appear in table 1. It is to be noted in particular that after the intracerebral pressure rose to within 50 to 20 mm. of mercury of the diastolic blood pressure (in all but experiments 1 and 8, table 1) the animal remained comatose for the rest of the experiment. In contrast to this constant correlation between intracerebral pressure and loss of consciousness, the amount of water perfused to attain this result varied considerably from one animal to another. Lack of correlation between the amount of water administered and the degree of swelling of the brain was first observed by Weed and McKibben[2] in cats. The exact mechanism by which water acts on brain tissue to produce its effects is not known. That the factors involved may vary from time to time even in the same animal was demonstrated strikingly by the following experiments performed on the same animal on succeeding days.

Experiment 1 (Nov. 27, 1941): Weight 6.9 Kg.; ether anesthesia.

Procedure: One hundred cubic centimeters of water per kilogram of body weight was perfused aseptically at a rate of 28 cc. per minute.

Result: Thirty minutes after the end of the procedure the animal was depressed but could walk around fairly well.

Experiment 2 (November 28): Same animal, now normal; ether anesthesia.

Procedure: Sixty cubic centimeters of distilled water per kilogram of body weight was perfused aseptically at a rate of 6.5 cc. per minute.

The difference in rate of perfusion in the two experiments may have been an important factor in causing the difference in results. That the results obtained are not solely dependent on the total amount of water perfused is here apparent.

Two control experiments were set up exactly like the other experiments of this series except that water perfusions were not made; the dogs were allowed to remain under anesthesia for four hours. In these animals the intracerebral and intraventricular pressures remained constant at low levels (approximately 10 mm. of mercury). The dogs regained consciousness twenty and thirty minutes respectively after removal of the ether at the end of the four hour period.

To distinguish more definitely between the effects of the perfusion of water and those of the rise in intracerebral and intraventricular pressures it entails, experiments were performed on animals to which no water was administered but in which the intracranial (intraventricular) pressure was raised mechanically by means of isotonic solution of three chlorides introduced by means of a pressure bottle.

2. Weed, L. H., and McKibben, P. S.: Am. J. Physiol. **48**:531, 1919.

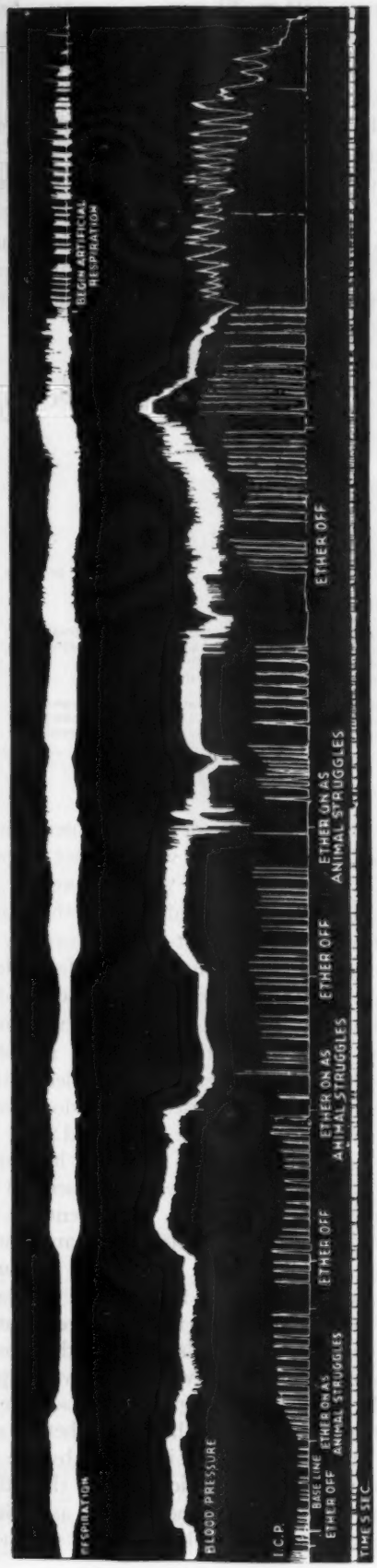

Fig. 1.—Water is perfused into the central (anatomic) end of the common carotid artery. When the intracerebral pressure (*I. C. P.*) reaches certain levels below the level of the diastolic blood pressure, death follows, as shown in the record.

SERIES 2 (8 experiments; 3 control experiments).—*Effect of elevation of the intraventricular pressure on consciousness in the dog.*

Procedure.—The animals used in this series were anesthetized with ether, placed on the abdomen and secured to the operating table. By means of a drill, a hole was made in the calvarium just large enough to allow an 18 gage needle, the tip of which had been filed flat, to be held securely in place by the surrounding bone when pushed through the brain tissue into the lateral ventricle. The appearance of clear cerebrospinal fluid at the opening of the needle was taken as proof that the tip was in the lateral ventricle. Isotonic solution of three chlorides, warmed to body temperature, could then be introduced directly into the cranial cavity by means of a pressure bottle, the pressure in which was measured by means of a mercury manometer. The blood pressure of the animal was measured through a cannula inserted into the left carotid artery; respiration was recorded with a pneumograph and a tambour.

After the animal had been completely prepared for experimentation, the ether was removed and the animal allowed to demonstrate its ability to regain consciousness by the aforementioned criteria. Then, once again, the animal was anesthetized and the intraventricular pressure raised to a level approximating that found efficacious for production of unconsciousness in the water perfusion experiments. In such animals, in which water was not perfused, the intracerebral pressure was close to the elevated level of the intraventricular pressure. After thirty minutes the ether was removed. The pressure was kept high for thirty to sixty minutes after removal of the ether, the entire period of increased pressure being sixty to ninety minutes (sixty minutes in 2 experiments, eighty minutes in 5 experiments and ninety minutes in 1 experiment).

Results.—A total of 8 such experiments were performed. None of the animals regained consciousness during the period of increased intraventricular pressure. Three control animals on which the same manipulations were performed except for the increase in intraventricular pressure regained consciousness twenty, fifteen and eighteen minutes respectively after the thirty minute period of anesthesia. All animals were kept under anesthesia sufficiently light so that the corneal reflex retained its activity.

At the end of the period of raised intraventricular pressure the pressure was reduced to zero and the animal was placed on the floor for observation. Two of the animals died four and a half and five hours respectively after the intraventricular pressure had been lowered. These were the dogs which received the greatest trauma in terms of height and duration of increased pressure. One of the animals did not regain any semblance of consciousness during the seven hour period of observation after reduction of the intraventricular pressure to zero. During this period the animal, lying on its side, kept up walking movements.

The remaining 5 animals regained enough functional ability to be able to stand up and walk, though somewhat incoordinately, at various intervals after decompression. The results appear in table 2, in which are shown values for blood pressure, intraventricular pressure, amount of time the intraventricular pressure was kept high and length of time after decompression before the animal regained a semblance of consciousness. The animals subjected to the lower intraventricular pressures in relation to their blood pressures regained functional ability most readily.

TABLE 2.—*Effect on Consciousness of Increased Intraventricular Pressure in Eight Dogs*

Experiment No.	Weight of Animal, Kg.	Blood Pressure, Mm. Hg	Level to Which Intraventricular Pressure Was Raised, Mm. Hg	Diastolic Blood Pressure Minus Intracerebral Pressure, Mm. Hg	Duration of Increased Intracerebral Pressure, Min.	Comment
1	9.1	248/204	168	36	60	Could walk around 1 hr. after decompression
2	10.4	158/134	94	40	60	Could crawl on haunches 20 min. after intracerebral pressure was lowered
3	18.2	158/144	112	32	80	Died 4½ hr. after decompression
4	22.7	148/130	100	30	80	Died 5 hr. after decompression
5	18.2	158/148	102	46	90	Still exhibited decorticate walking 7 hr. after decompression
6	13.6	162/128	90	38	80	Could sit up and look about 3½ hr. after decompression
7	25	158/138	100	38	80	Could walk around 1 hr. after decompression
8	15.8	152/136	92	44	80	Could walk around 1 hr. after decompression
Controls:						
1	25	150/130	0	..	..	Regained consciousness 20 min. after ether was removed
2	20	160/135	0	..	..	Regained consciousness 15 min. after ether was removed
3	15.8	140/122	0	..	..	Regained consciousness 18 min. after ether was removed

A protocol of a typical experiment follows.

Dog 8: Weight, 15.8 Kg.

Time (P. M.)	
4:00	Animal set up completely; ether removed.
4:22	Animal struggled; ether administered.
4:30	Intraventricular pressure raised and kept at 44 mm. of mercury below diastolic blood pressure.
5:00	Ether removed.
5:20	Animal shivering, somewhat tense; good corneal reflex; animal lying quietly; stertorous respiration.
5:30	Head lifted and turned to left; back slightly arched, owing to rigidity of muscles of neck and back; animal breathing heavily; forelimbs somewhat extended; hindlimbs in more or less normal position.
5:40	Head still raised.
5:45	Intraventricular pressure lowered to zero.
5:50	Animal lying on floor; limbs half flexed; back somewhat arched; respiration 100 per minute and stertorous.
6:05	Animal lying on laboratory floor and shivering; limbs not extended; breathing heavy; nystagmus to the left.
6:15	Animal succeeded in turning onto abdomen after several attempts; still more pronounced nystagmus to left and head turned half to left.
6:25	Animal could now stand up and walk incoordinately round room; dog then killed.

These experiments demonstrate the effect of raised intraventricular pressure on the "conscious activity" of the animal. The levels of pressure utilized in these experiments (30 to 45 mm. of mercury below the diastolic blood pressure) were approximately the same as the levels of intracerebral pressure associated with loss of consciousness in the water perfusion experiments (50 to 20 mm. of mercury below diastolic blood pressure), so that the possible role the water itself may have played in the loss of consciousness was thus ruled out. As previously stated, in an animal not subjected to perfusion of water the intracerebral pressure was close to the elevated level of the intraventricular pressure. As can be seen in the protocol cited on page 510, the intraventricular and intracerebral pressures of an animal in which water had been perfused may differ by a number of millimeters of mercury.

COMMENT

As previously stated, these experiments were undertaken to determine what effect experimentally produced edema would have on the conscious state of the animal. From the resulting evidence it is apparent that failure of the animal to regain consciousness, by the criteria here employed, was more or less independent of the amount of water perfused and was more directly dependent on the elevation in intracerebral pressure this perfusion entailed. If it is assumed that the perfused water does cause cerebral edema, it must be concluded that the effect on consciousness was more or less independent of the amount of edema produced in the brain and was more directly dependent on the coincident increase in intracerebral and intraventricular pressure. The increase in pressures bore no strict relation to the amount of water perfused in each case, but the pressures (intracerebral and intraventricular) reached through perfusion of water which were effective in preventing the animal from regaining consciousness after removal of the ether anesthetic also produced unconsciousness in the absence of water perfusion. This indicates that the effect on the conscious state of the animal, as judged by the criteria here employed, was produced

through the action of the intracerebral pressure itself, and not through the action of distilled water itself.

The rise of the intracerebral and the intraventricular pressure above the cisternal pressure was dependent on the production of an internal hydrocephalus consequent to perfusion of water. The mechanism of production of this hydrocephalus will be more thoroughly discussed in part II.

ventricular pressures rose above the cisternal pressure and that after certain levels of pressure were reached (60 to 20 mm. of mercury below the diastolic blood pressure) the experimental animals no longer regained consciousness when allowed to exhale the volatile anesthetic.

When the intracerebral and intraventricular pressures approached the level of the diastolic blood pressure, death resulted from respiratory and circulatory failure.

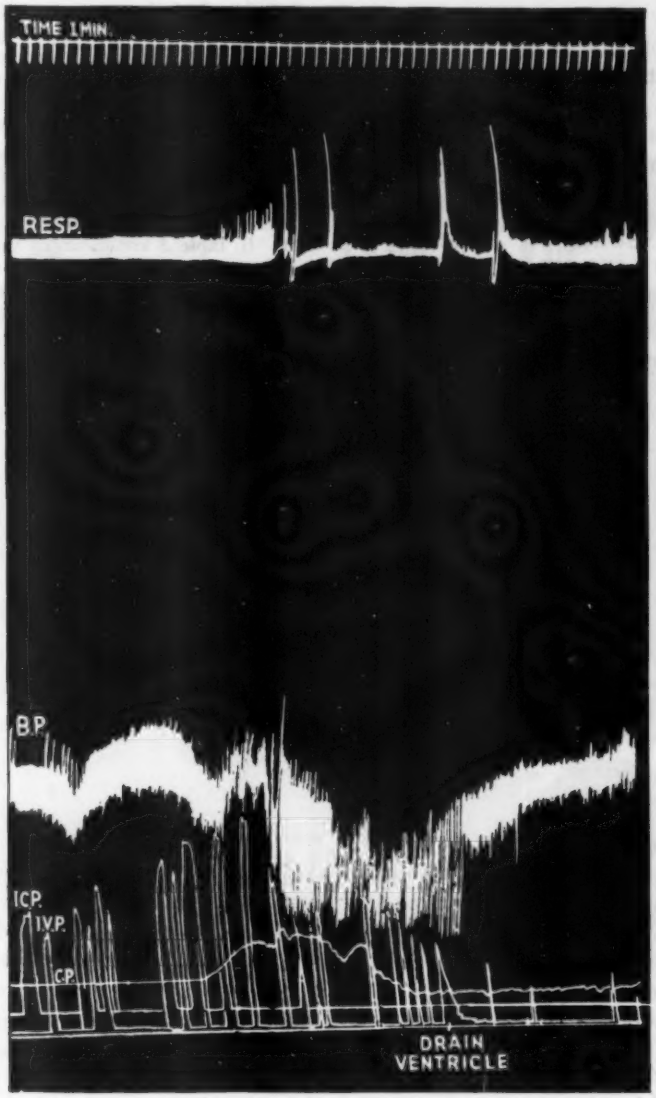

Fig. 2.—When the intraventricular and the intracerebral pressure reach the height shown here, and with a relatively low cisternal pressure, the respiratory and circulatory effects illustrated here occur. The animal is restored to normal when the intraventricular and the intracerebral pressures are lowered, as indicated here.

SUMMARY AND CONCLUSIONS

By a method of measurement of pressure in the brain tissue (intracerebral pressure) described here it was found that consequent to perfusion of water the intracerebral and intraventricular pressures rose above the cisternal pressure and that after certain levels of pressure were reached (60 to 20 mm. of mercury below the diastolic blood pressure) the experimental animals no longer regained consciousness when allowed to exhale the volatile anesthetic.

If the cisterna magna was allowed to be open to the exterior after the intracerebral and the intraventricular pressure had risen somewhat above the cisternal pressure, the heights to which the former rose were not affected.

Prior to perfusion of water the intracerebral pressure bore a close relation to the intraventricular pressure; after perfusion of water this pressure in many cases differed by several millimeters of mercury from the intraventricular pressure.

If in animals not subjected to perfusion of water the intraventricular pressure was raised to the levels associated with unconsciousness in the water perfusion experiments, unconsciousness resulted.

It is concluded that the effect on consciousness here produced was directly dependent on the level of intracerebral pressure itself, and not directly on the action of the water itself.

II. EFFECTS OF INCREASED INTRAVENTRICULAR PRESSURE ON RESPIRATION AND CIRCULATION

In part I the effects of perfusion of distilled water into the anatomic central end of the common carotid artery are described. This procedure resulted in elevation of the intracerebral and intraventricular pressures to levels above the cisternal pressure. When the intracerebral and the intraventricular pressure approached the level of the diastolic blood pressure, dire respiratory and circulatory effects were produced, ending in the death of the animal. Respiration first became labored and then stopped, and circulatory failure was preceded by pronounced slowing of the pulse (heart rate) and terminal hypertension in 50 per cent of the experiments.

The experiments now to be reported on were undertaken to study more closely the mechanism involved in production of these effects on respiration and circulation.

EXPERIMENTAL OBSERVATIONS

SERIES 1 (10 experimental animals).—*Effect on respiration and circulation of perfusion of water into the brain.*

Procedure.—The animal was placed on its side, with the head in a normal or a slightly flexed position. The cisternal and the blood pressure were measured by means of a mercury manometer, as in the water perfusion experiments previously described; respiration was recorded by the usual pneumograph-tambour method, and the intracerebral and intraventricular pressures were measured by the device previously described (part I). Distilled water was perfused by hydrostatic pressure.

Distilled water was perfused through the anatomic central end of the same carotid artery from which the blood pressure was being measured. As perfusion of water progressed, the intracerebral and the intraventricular pressures rose above the cisternal pressure, the cisterna magna being opened to the exterior at various intervals after the beginning of the perfusion in 5 of these experiments. Respiratory and circulatory embarrassment appeared when the intracerebral and intraventricular pressures reached certain levels, at which time the procedures to be described were carried out. In table 3 are recorded the levels of intracerebral, intraventricular and cisternal pressures associated with the onset of circulatory and respiratory difficulties in this series. The intraventricular pressure is subtracted from the diastolic blood pressure here for purposes of comparison with the later series.

TABLE 3.—*Levels of Intracranial Pressure Associated with Onset of Respiratory and Circulatory Effects in Eleven Dogs Receiving a Perfusion of Water*

Experiment No.	Weight of Animal, Kg.	Amount of Water Used, Cc./Kg.	Intracerebral Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Cisternal Pressure, Mm. Hg	Blood Pressure	Diastolic Blood Pressure Minus Intraventricular Pressure
1	10	60	76	62	39	110/ 90	28
2	17.3	58	72	70	0	160/100	30
3	19.1	63	140	140	0	220/210	60
4	9.1	121	110	105	84	186/152	48
5	10.4	140	...	90	39	138/125	35
6	11.8	85	110	98	0	138/124	26
7	7.3	110	76	72	0	120/108	36
8	9.5	105	68	60	0	145/122	62
9	9.5	105	72	75	24	140/106	31
10	7.3	110	50	50	0	150/100	50
Average	11.1	95.7	86	82.2	..	150/123	40.8

Results.—1. When the blood pressure and respiration were about to fail, a syringe needle was inserted into the lateral ventricle and fluid was removed. This resulted in a sharp decrease in the intracerebral and intraventricular pressures and in immediate improvement in respiration and circulation. Figure 2 illustrates this. Here drainage of the ventricle resulted in lowering of the intraventricular pressure from 98 to 16 mm. of mercury and in lowering of the intracerebral pressure from 90 to 17 mm. of mercury.

2. When the cisternal pressure was raised by fluid introduced through the cisternal needle to levels equal to or above those attained in the cranial cavity (intraventricular and intracerebral pressures) when the blood pressure and the respiration began to fail, no ill effects or changes in blood pressure or respiration resulted. The intraventricular and intracerebral pressures were raised to levels just under cisternal pressure by

this procedure, presumably owing to refilling of the ventricles by the fluid introduced into the cisterna magna. This effect is illustrated in figure 3, which will be described shortly in more detail.

3. If the cisterna magna was then opened to the exterior, the intracerebral and intraventricular pressures remained at the same level as or rose to higher levels than those to which they were elevated by the procedure described in *2*, the fluid now being trapped in the ventricles. This condition of high intraventricular pressure and low cisternal pressure again resulted in respiratory and circulatory embarrassment. This effect is illustrated in figure 3. The ability of fluid to get into the ventricles through the cisterna magna but not out after cisternal drainage in such edematous brains, is most important. In 2 of the animals the lowering of the cisternal pressure was more gradual but gave rise to the same consequences.

4. Drainage of the ventricles after the medullary centers were subjected to the treatment described in *3* had the following results:

(*a*) In 4 animals the fall in blood pressure was checked, and after a few minutes of artificial respiration they began to breathe spontaneously. The blood pressure rose but stopped at lower levels than were held prior to insult to the pressor centers in the medulla. This is illustrated by figure 3, which will now be described. At *A*, the respiration, which had stopped after high levels of intraventricular and intracerebral pressures had been reached by water perfusion, was brought back to normal levels by ventricular drainage. The intracerebral pressure dropped from 60 to 22 mm. of mercury. Artificial respiration by tracheal insufflation kept the animal alive until drainage was completed and spontaneous respiration began. At *B*, after the blood pressure had attained a fairly normal level (150 systolic and 140 diastolic), increase in the cisternal pressure to 110 mm. of mercury for over twelve minutes did not result in respiratory or circulatory difficulties. The intracerebral pressure was increased to 90 mm. of mercury by this procedure. At *C*, the cisternal pressure was reduced to zero, but the intracerebral pres-

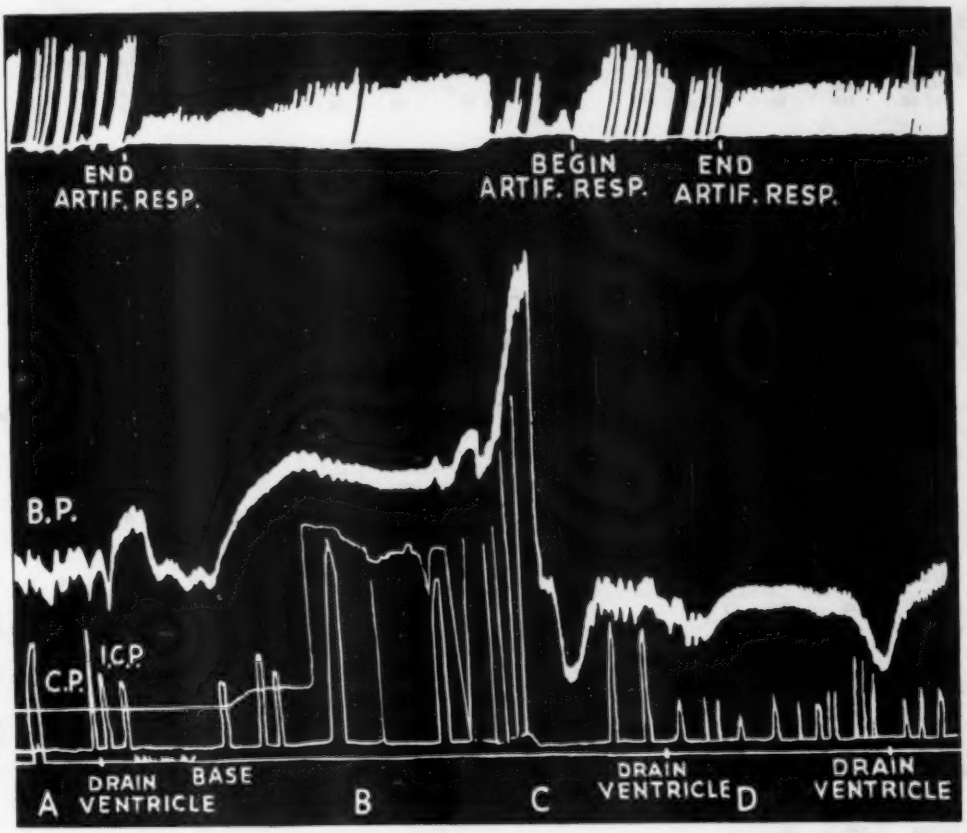

Fig. 3.—The record is more fully explained in the text. Essentially, it shows that there are no dire respiratory or circulatory effects when both the intracerebral and the cisternal pressure are elevated, but such effects occur if the cisternal pressure alone is lowered, leaving the intracerebral and intraventricular pressures elevated.

sure not only remained high but was somewhat higher than before the cisternal pressure was lowered. In two minutes respiration ceased and the blood pressure, after rising rapidly to a peak of 250 systolic and 240 diastolic, dropped sharply. It may be noted how the intracerebral pressure rose and fell with the blood pressure. The rapid descent of the blood pressure was checked by the institution of artificial respiration, and when, at *D*, the lateral ventricle was again drained, the intracerebral pressure dropped from 50 to 14 mm. of mercury and respiration again became spontaneous. The blood pressure had now dropped to a much lower level (90 systolic and 78 diastolic) and was very sensitive to increased intraventricular pressure, vasomotor failure occurring when the intracerebral pressure was raised to 38 mm. of mercury. The blood pressure recovered from the last drop on drainage of the ventricle, the intracerebral pressure being brought to 26 mm. of mercury. The rise in intracerebral pressure here was due to bleeding into the ventricle brought about by the trauma consequent to the ventricular drainage in this case. Although in this part of the experiment the intraventricular pressure was not simultaneously recorded, one may assume from values obtained in other experiments that it paralleled the intracerebral pressure fairly closely (in the absence of subdural hematoma).

(*b*) In 4 animals ventricular drainage resulted in improvement of respiration and a check in the rate of lowering of the blood pressure, but the circulation continued to fail, although the intraventricular pressure was kept very low by drainage. These animals died of circulatory failure.

TABLE 4.—*Effects on Respiration, Blood Pressure and Heart Rate of Elevation of*

	Control				Cisternal Pressure Elevated						Intraventricular			
Experiment No.	Blood Pressure	Heart Rate per Min.	Respiratory Rate per Min.	Respiratory Amplitude per Min.	Elevated Level of C. P. Mm. Hg	Reading Time of C. P. After Elevation, Min.	Blood Pressure	Heart Rate per Min.	Respiratory Rate per Min.	Respiratory Amplitude per Min.	Elevated Level of I. V. P., Mm. Hg	C. P., Mm. Hg	First Reading Time (Min.) After Elevation of I. V. P.	Blood Pressure
1	94/ 86	152	44	6.5	..	..	.....	..	..	..	63	8	1	90/ 56
2	104/ 92	108	36	12.5	72	1	110/ 88	96	24	9	64	2	1	104/ 90
3	144/136	180	56	7	..	..	.....	...	..	..	104	6	0.5	120/100
4	102/ 92	152	41	5	..	..	.....	..	..	..	65	4	1	110/ 94
	115/104	132	44	3.5	..	..	.....	..	..	..	70	5	1	120/106
5	150/136	148	41	5	85	3	138/122	148	37	5	79	0	1	134/120
											71-77	0	1	151/138
	142/128	128	72	7	77	2	148/136	128	66	9	76	0	1	148/132
	152/137	148	45	9	..	..	.....	...	..	..	130	0	20 sec.	130/102
	150/130	148	28	6	77	1	148/135	148	49	7	78	0	1	136/114
											76	0	1	136/114
	158/140	112	72	10	128	1	178/146	84	28	7	120	4	1	170/133
									36	2	50-55	0	1	64/ 60
6	64/ 56	148	40	1	34	1	70/ 64	148	..	..	58	5	1	90/ 80
7	96/ 85	128	22	11	..	..	.....	...	..	..	56	0	1	82/ 74
											50	0	1	96/ 80
8	106/ 98	184	42	10	..	..	.....	...	..	..	59	12	3	102/ 90
	123/113	164	40	11	..	..	.....	...	..	..	65	28	1	134/ 96
9	.....	...	..	...	80	3	126/134	86	20	4.5	75-63	23-16	1	130/ 90
											78	22	3	134/ 94
10	132/120	184	34	3	..	..	.....	...	..	..	102	54	0.5	132/120
											82	60	1	114/102
											84	43	1	126/113
11	90/ 80	90	70	4	46	1	90/ 83	88	60	2	50	0	2	88/ 72
12	158/147	170	64	6	..	..	.....	...	..	..	90-82	3	4	158/146
13	130/118	176	68	5	106	3	140/130	168	48	5	..	..	..	.....
	116/106	160	56	6	..	..	.....	...	..	..	68	28	1	90/ 82
	100/ 90	156	44	5	..	..	.....	...	..	..	70	26	1	86/ 80
14	118/102	140	44	9	..	..	.....	...	..	..	64	18	1	118/ 92
											67	12	6	94/ 80

* In this table, C. P. indicates cisternal pressure, and I. V. P., intraventricular pressure.

(c) In 2 animals, after failure of respiration as a consequence of high intraventricular and low cisternal pressure, drainage of the ventricles was accomplished. Artificial respiration was administered, but 1 of the animals did not begin to breathe until eighty-five minutes later and the other until ninety minutes later. When respiration finally did begin, the blood pressure, which had been gradually declining and continued to fall slowly after respiration was restored, was checked in its descent and was definitely improved by the infusion of 500 cc. of isotonic solution of three chlorides into the central end of the carotid artery.

5. In 2 animals, when the intracerebral and intraventricular pressures had risen far enough above the cisternal pressure to produce respiratory and circulatory embarrassment, an attempt was made to raise the cisternal pressure above the intraventricular and the intracerebral pressure in order to ascertain whether this would result in improvement of respiration and circulation. It was found impossible to raise the cisternal pressure above the intracerebral and intraventricular pressures in these animals because as the cisternal pressure was raised the intracerebral and intraventricular pressures increased and remained above the cisternal pressure.

Intraventricular Pressure with Increase and with Decrease of the Cisternal Pressure *

Pressure Only Elevated								Cisternal Pressure Elevated to Level of Intraventricular Pressure (Except Where Indicated)						
Heart Rate per Min.	Respiratory Rate per Min.	Respiratory Amplitude per Min.	Second Reading Time (Min.) After Elevation of I. V. P.	Blood Pressure	Heart Rate per Min.	Respiratory Rate per Min.	Respiratory Amplitude per Min.	Elevated Level of C. P., Mm. Hg	Reading Time (Min.) After Elevation of C. P.	Blood Pressure	Heart Rate per Min.	Respiratory Rate per Min.	Respiratory Amplitude per Min.	Diastolic Blood Pressure Minus I. V. P. Employed
56	32	10	3	94/ 64	80	28	8	0	5	94/ 86	150	35	7	23
96	Complete inhibition		..	.....	...	..	..	I. V. P. lowered to 0	1	106/ 90	116	38	12	24
100	Complete inhibition		..	.....	..	..	..	I. V. P. lowered to 0	1	152/140	176	44	12	32
105	18	3.5	3	120/ 90	92	Complete inhibition		I. V. P. lowered to 0	2	110/ 98	152	40	7	27
120	25	4	3	98/ 84	120	Great depression to inhibition		..	3	116/104	124	32	3.1	34
128	40	4	10	148/134	144	Complete inhibition		76	3	143/132	172	52	2.2	57
178	44	2	3	152/140	172	24	1.2 †	78	3	150/140	184	20	5	52
116	64	7	9	155/122	84	Cheyne-Stokes respirations		80	4	146/132	120	70	8	56
90	Inhibition		..	.....	..	..	..	0	1	160/142	128	44	6	7
116	Cheyne-Stokes breathing		..	.....	..	..	..	80	1	150/136	144	56	6.5	57
108	Cheyne-Stokes respiration to inhibition for over a minute, when C. P. was raised, with recovery											..	..	38
66	Inhibition		..	.....	..	..	..	122	6	178/144	88	40	5	26
156	40	1	3	72/ 66	132	Inhibition		58	1	90/ 82	176	20	2	10
148	14	2	3	88/ 80	112	Inhibition; no recovery by		0	10	72/ 70	200	17	5	14
97	14	6	3	76/ 58	56	Complete inhibition		raising C. P., so C. P. lowered to 0 50	2	98/ 80	84	23	11	29
84	6	7	3	90/ 70	70	Complete inhibition		56	5	98/ 74	96	10	11	30
132	24	4	6	86/ 73	114	Complete inhibition		60	Artificial respiration necessary; only slight tendency to spontaneous recovery					39
140	16	2	7	96/ 76	100	8	1	58	3	120/ 90	74	8	7	47
58	14	3	3	130/ 90	60	Depression and Cheyne-Stokes breathing		76	1	134/110	86	20	5	59
64	Inhibition; no recovery when C. P. was raised; C. P. and I. V. P. lowered; artificial respiration given												..	32
132	All but complete inhibition		..	.....	..	..	..	92	1	138/128	128	17	2	18
128	14	1.5	..	.....	..	..	..	76	1	122/112	124	16	2	50
114	16	2	..	.....	..	..	..	90	3	128/116	128	18	2.8	28
80	Inhibition		..	.....	..	..	..	43	1	96/ 88	90	64	3	33
132	44	5	7	156/ 40	118	Cheyne-Stokes respiration to inhibition		83	1	184/ 68	136	45	8	57
144	33	4	3	82/ 74	160	29	4	0	3	94/ 82	148	44	7	38
160	20	1	3	86/ 81	172	Great depression to inhibition		..	..	.....	...	..	..	20
116	47	8	3	120/100	124	48	6	67	3	106/ 94	160	35	5	38
116	28	5	..	.....	...	..	..	60	2	94/ 82	138	25	6	27

† Respiration was inhibited in three minutes; cisternal pressure was raised to 78 mm., and artificial respiration was diminished.

	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg
Animal 8	0	60	68
Cisternal pressure raised to	80	94	..
Cisternal pressure lowered to	0	50	56
Animal 10	0	56	62
Cisternal pressure raised to	84	96	100
Cisternal pressure lowered to	0	66	70

But if when the cisternal pressure was raised the ventricles were drained so as to bring the intraventricular pressure down to meet the cisternal pressure, despite the fact that the latter was raised (and the intraventricular and intracerebral pressures with it) to a level which had just caused respiratory and circulatory embarrassment, the respiration and circulation improved, a result demonstrating that to have the intraventricular pressure and the intracerebral pressure higher than the cisternal pressure is more deleterious than to have both the cisternal and the intraventricular pressure at even higher levels. Figure 4 illustrates this observation.

To rule out the effects of water perfusion on the results in series 1, a study was now made of the effects of producing a large disparity in pressure between the ventricular and the spinal fluid reservoir in normal animals.

SERIES 2 (29 experiments on 14 animals).—*Effects on the circulation and respiration of large differences in pressure between the ventricles and the spinal subarachnoid spaces.*

High Intraventricular and Low Cisternal Pressures.—The following procedure was observed:

After etherization the animal was placed on the abdomen, with the head extended, and secured to the operating table. An attempt was made to keep the animal at the second plane of the third stage of anesthesia. A small hole was made in the calvarium, through which a 14 gage, flat-tipped copper needle could be passed and forced through the brain tissue into the anterior portion of the lateral ventricle. The appearance of clear cerebrospinal fluid at the opening of the needle was taken as evidence of the proper location of the needle. Once in place, the needle was kept so by the closely surrounding bone of the calvarium. Through this needle isotonic solution of three chlorides, warmed to body temperature, was perfused into the lateral ventricle by means of a pressure bottle. This perfusion pressure was recorded on a kymograph with a mercury manometer.

A second hole was made in the calvarium somewhat posterior to the first so that an 18 gage, flat-tipped needle could be passed through and into the posterior part of the lateral ventricle. Through this needle the pressure in the lateral ventricle was measured by means of a mercury manometer. Through the muscles of the neck and the occipitoatlantal ligament and into the spinal subarachnoid space adjoining the cisterna magna, two needles were passed. Extension of the head, so that the occipital condyles and the atlas were brought closer together, served to hold these needles in place. The smaller of the two needles, an 18 gage, was connected by means of rubber tubing to a mercury manometer, and the spinal fluid pressure was measured at the needle's tip. The larger needle, a 16 gage, was fitted with a metal plug, which could be easily removed or replaced. On removal of the plug the cerebrospinal fluid from the cisterna magna could easily flow to the exterior.

It was thus hoped that the combination of rapid infusion through the large ventricular perfusing needle, the resistance to the passage of fluid to the cisterna magna offered by the aqueduct of Sylvius and the rapid drainage away from the cisterna magna of the incoming fluid would result in the creation of large differences in pressure between the two reservoirs of fluid. In animals in which the resulting difference in pressure was not great, an attempt was made to add resistance to the flow of fluid through the aqueduct of Sylvius by introducing small bits of brain tissue, retained from a previous experiment, through the perfusion needle into the lateral ventricle. As these bits were being introduced, the intraventricular pressure was prevented from rising by keeping the spinal drainage needle patent. Although not always efficacious, this method succeeded in 4 of the experiments in producing a complete block between the ventricular and the spinal fluid reservoir—presumably by complete obstruction of the aqueduct of Sylvius. The blood pressure and the respiration were recorded as in previous experiments.

Twenty-nine experiments were performed on 14 animals. The procedure consisted in elevation of the intraventricular pressure to levels varying from 60 to 10 mm. of mercury below the diastolic blood pressure and observation of the effects on respiration, blood pressure and heart rate. Such pressure levels were those associated in the preceding series with the onset of circulatory and respiratory difficulties. The results are presented in table 4. After definite effects of the high intraventricular pressure were noted, in 23 of the experiments the cisternal pressure was raised to the level of the intraventricular pressure. This resulted in improvement of the animal's condition. In 6 of the experiments lowering of the intraventricular pressure to zero resulted in restoration of the blood pressure and respiration toward normal. Such increases and decreases in cisternal pressure while the intraventricular pressure remained high serve to emphasize the difference in action of high intraventricular pressure alone, on the one hand, and of high intraventricular and high cisternal pressure, on the other. The results of these experiments are now presented.

Respiratory Effects: The respiratory effects were the most striking, and in most instances set the limit to the period of elevated intraventricular pressure. In 22 of the 29 experiments the respiration first became depressed and then completely inhibited in the course of twenty seconds to ten minutes, the time depending in general on the height of the intraventricular pressure. Respiration became inhibited in twenty seconds when the intraventricular pressure was raised to within 7 mm. of mercury (mercury manometer) of the diastolic blood pressure and in ten minutes when it was 57 mm. of mercury (mercury manometer) below the diastolic blood pressure. In the same animal, when more than 1 experiment was performed, the respiration became inhibited much earlier in the later experiments than after the first elevation of the intraventricular pressure. After the respiration had ceased or had become Cheyne-

Stokes in character, either a decrease in the intraventricular or an increase in the cisternal pressure to the level of the intraventricular pressure resulted in rapid improvement of the respiration. Figures 5 and 6 illustrate this. In some experiments artificial respiration was administered until spontaneous respiration returned. The data from these experiments are also indicated in table 4. In the remaining 7 experiments, although the intraventricular pressure did not remain high long enough to cause inhibition of respiration, definite depression in rate and amplitude occurred. In all experiments the depression of respiration was associated with a change to the abdominal type.

Cardiac Effects: As previously pointed out, the time limit of the experiments was set by the respiratory effects, and hence what might have happened to the cardiac rate if the experiments had continued longer is not known. The possibility that further adjustment to the effects of high intraventricular pressure well might have taken place if the experiments had been prolonged must be kept in mind. The cardiac changes and the time of their occurrence after elevation of the intraventricular pressure appear in table 4.

In 21 of the 29 experiments, cardiac slowing occurred during the period of increased intraventricular pressure. In general the higher the level of the intraventricular pressure, the greater the slowing of the heart, vagal beats appearing after a short period at the highest levels of pressure. In 4 experiments the initial slowing of the heart rate was followed by a tendency to a return to normal as the experiment proceeded, the control rate being reached in 1 experiment. In 2 experiments a slight initial increase was fol-

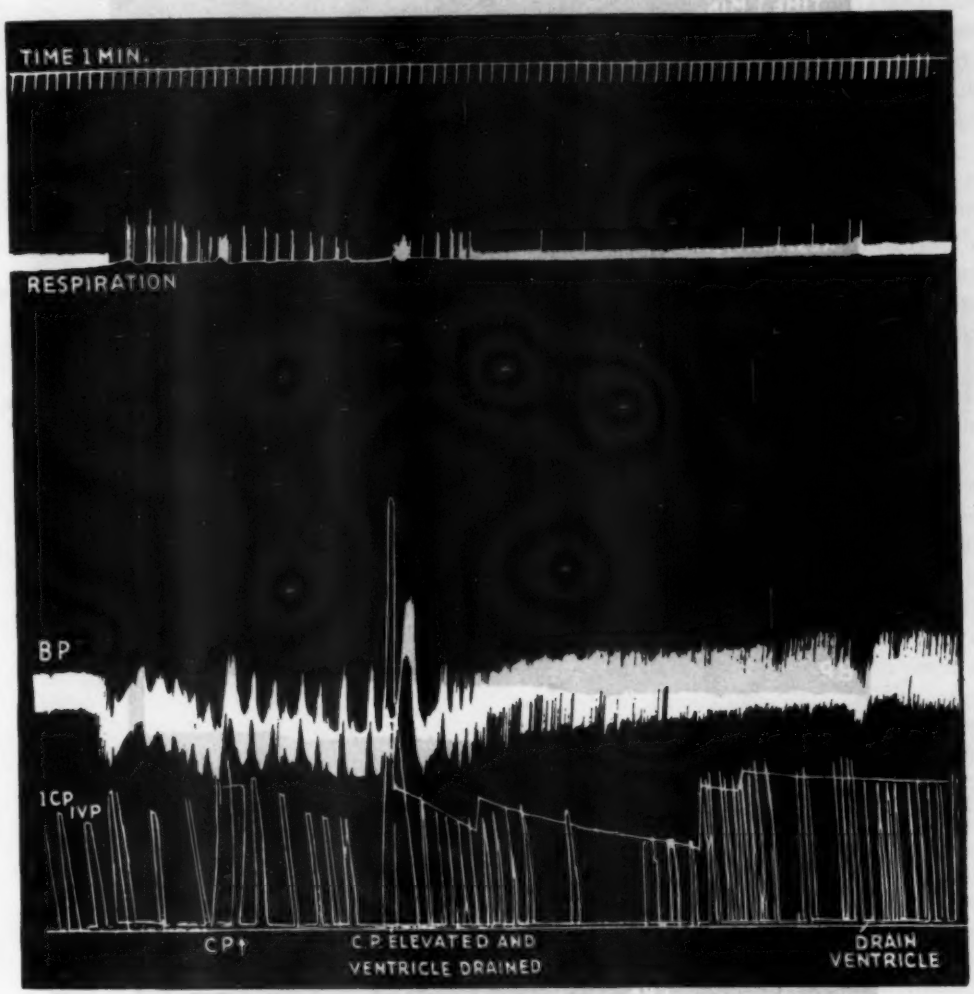

Fig. 4.—With the cisternal pressure at zero and the intraventricular and intracerebral pressures moderately elevated, respiration and circulation become embarrassed. They are restored toward normal by elevation of the cisternal pressure to the level of the intraventricular and intracerebral pressures.

lowed by a slowing in rate, the intraventricular pressure in 1 of them being but 10 mm. of mercury (mercury manometer) below the diastolic blood pressure. In 1 experiment the heart rate continued to increase during the period of increased intraventricular pressure, the pressure in this experiment being but 20 mm. of mercury below the diastolic blood pressure. In 1 experiment no change occurred during the period of the test. In all experiments, with few exceptions, either lowering of the intraventricular pressure to zero or elevation of the cisternal pressure to the level of the intraventricular pressure resulted in return of the heart rate toward the control level.

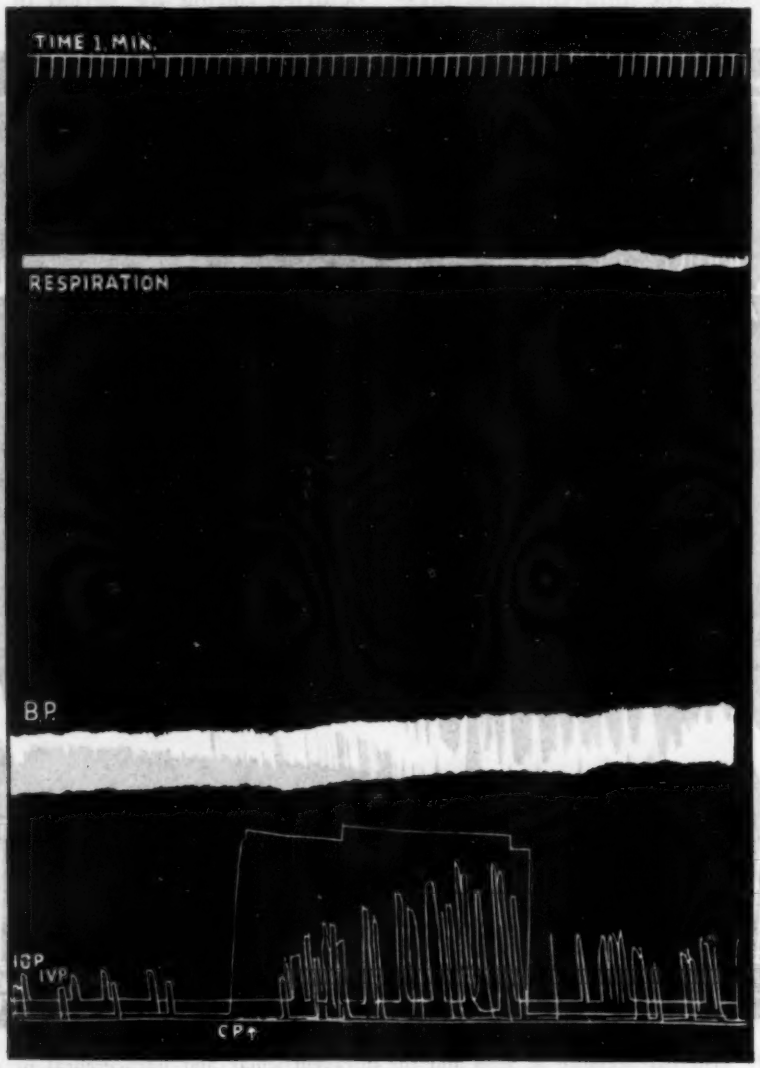

Fig. 5.—In this animal for the first twelve minutes after cisternal pressure was elevated, the intraventricular pressure and the intracerebral pressure remained relatively low. There were no marked effects on the blood pressure or the respiration.

Hemodynamic Effects: The time limit set by the respiratory effects prevented a study of the effects on the blood pressure of more prolonged exposure to high intraventricular pressure. Further studies on the effects of a slow increase in the intraventricular pressure over longer periods than were involved here would be of value in this connection. The hemodynamic effects in the present acute experiments were in general neither striking nor constant. In 15 experiments some depression of blood pressure occurred during the elevation of intraventricular pressure (of between one and six minutes' duration). In 5 experiments the tendency was toward a rise in blood pressure. In 2 experiments there was an initial fall in blood pressure followed by recovery to normal control levels. In 2 experiments there was an initial increase followed by a tendency toward depression of the

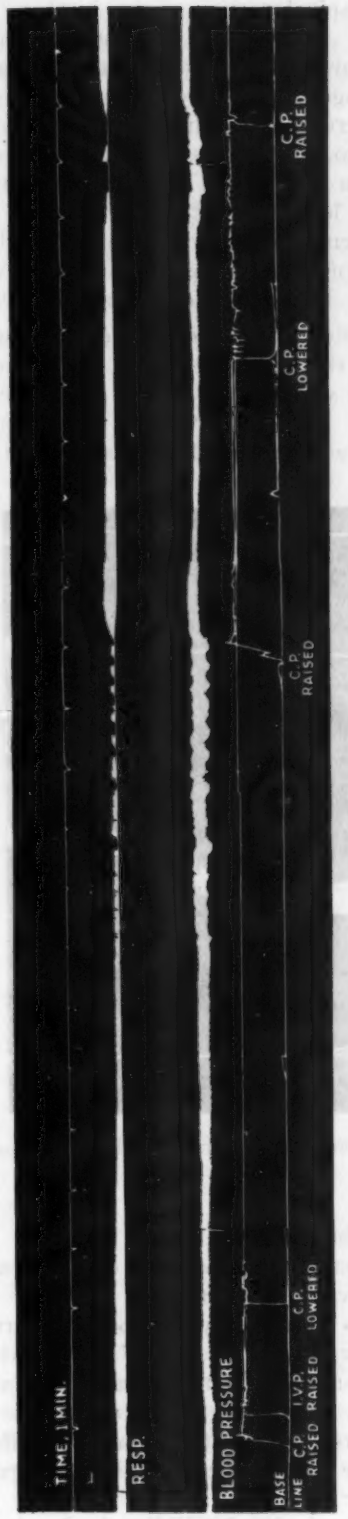

Fig. 6.—Effects on blood pressure and respiration of variation in the intraventricular and the cisternal pressure independently.

blood pressure. In 5 experiments no change in blood pressure occurred during the period of elevation. No correspondence was noted between the character of the hemodynamic effect and the level of the intraventricular pressure. In the experiments in which the cisternal pressure was raised to the level of the intraventricular pressure or the latter was lowered to zero, the blood pressure showed a tendency to return to control levels.

High Cisternal and Low Intraventricular Pressure.—A bit of information concerning the reverse condition of a high cisternal and a low intraventricular pressure was incidentally furnished in 4 experiments of the water perfusion series in which, for some reason, in the course of preparation the patency between the cisterna magna and the ventricles was in some measure interfered with, so that the filling of the ventricles from the cisterna magna was delayed for several minutes. Unfortunately, on these occasions the tracings were taken on a rather slow drum, so that changes in the heart rate and the respiratory rate were not recorded. That no striking changes in these rates took place was evident, however, as was the absence of any effect on the amplitude of respiration and the blood pressure. Table 5 indicates the blood pressure, the cisternal pressure, the intraventricular pressure and the time, expressed in minutes, that the cisternal pressure was high while the intraventricular pressure was low. Figure 7 is the record obtained from an experiment performed on September 14. In this experiment the cisternal pressure was abruptly raised to 96 mm. of mercury, while during the first eight minutes the intraventricular pressure rose from 18 to 40 mm. and the intracerebral pressure from 16 to 40 mm. of mercury. The value of the pressure in the carotid artery at this time was 145 systolic and 116 diastolic. As can be seen, these first eight minutes were associated with little or no effect on the blood pressure or the respiration. In the remaining twelve minutes the intraventricular pressure rose from 40 to 64 mm. and the intracerebral pressure from 40 to 64 mm. of mercury. The latter period was associated with a slight decrease in amplitude of respiration. These records were obtained before water perfusion was begun. Although far from complete, these data show that for the pressures involved adjustment to the state of high cisternal and low intraventricular pressure was much more easily made by the medullary centers than was adjustment to the state of high intraventricular and low cisternal pressure. Of interest in figure 7 is evidence of a

phenomenon noted in all the normal animals worked with, namely, that the intracerebral pressure does not rise directly with the cisternal pressure but is directly dependent on the filling of the ventricles and that its magnitude approximates the ventricular pressure.

TABLE 5.—*Data on Four Experiments in Which Cisternal Pressure Was High and Intraventricular Pressure Was Low*

Date	Time (Min.) That Difference Between Cisternal and Intraventricular Pressure Was Maintained	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Blood Pressure, Mm. Hg	Diastolic Blood Pressure Minus Cisternal Pressure, Mm. Hg
7/23/42	7.5	100	50	140/120	20
7/24/42	5	100	20	164/155	55
8/10/42	7	70	30	130/120	50
9/14/42	8	96	18 to 40	145/116	20

Ordinarily adjustment to changes in blood volume in the brain tissue may take place by displacement through the foramen magnum and into the spinal portion of the dural sac of cerebrospinal fluid from the subarachnoid and ventricular fluid reservoirs in the cranial cavity. The changes in pressure of the brain tissue and of the cerebrospinal fluid of normal dogs consequent to intravenous injection of epinephrine are shown in table 6. The rise in systemic blood pressure leads to increased cerebral volume. This dependence of the volume of the brain on the level of the systemic blood pressure was first shown by Roy and Sherrington [4] in 1898.

Normally in the dog the communication between the ventricles and the spinal subarachnoid spaces is not as free as was heretofore thought. This has recently been shown by Meyers,[5] who measured simultaneously the pressure in the cisterna magna and that in the lateral ventricles. That the cisternal and the intraventricular pressure may differ by several millimeters of mercury has been confirmed in the present work. In table 7 are listed values for the cisternal and the intraventricular pressure taken at random during the course of the experiments. Within these limits of differences in pressure the ventricular fluid is trapped in a

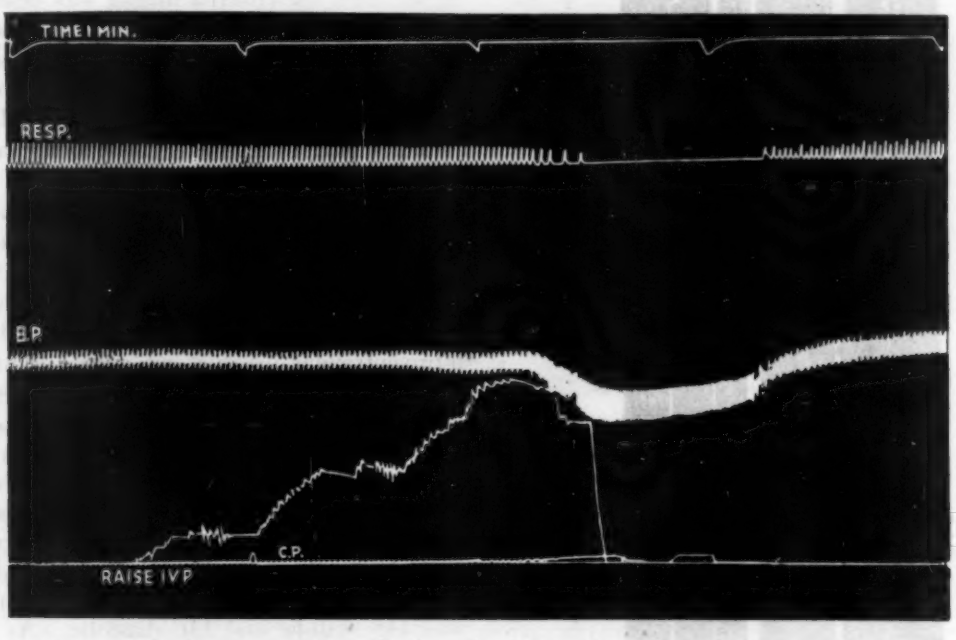

Fig. 7.—Effect on blood pressure and respiration of raising and lowering the intraventricular pressure while the cisternal pressure remains at zero.

INTRACRANIAL MECHANICS

The addition to the Monro-Kellie doctrine of the concept of limited elasticity of the dural sac was based on ample experimental evidence.[3] This "give" in the dural sac has been attributed to contraction and expansion of the spinal portion, with reciprocal changes in the epidural space and at the occipitoatlantal ligament.

3. Flexner, L. B.; Clark, J. H., and Weed, L. H.: Am. J. Physiol. **101**:292, 1932. Weed, L. H.: Some Limitations of Monro-Kellie Hypothesis, Arch. Surg. **18**:1049 (April) 1929. Weed, L. H.: Physiol. Rev. **13**:80, 1933.

4. Roy, C. A., and Sherrington, C. S.: J. Physiol. **11**:85, 1890.

5. Meyers, R. J.: J. Neuropath. & Exper. Neurol. **1**:241, 1942.

closed system; consequently, it might be expected that the intraventricular pressure would vary independently of cisternal pressure in response to changes in cerebral volume within such limits. The data in table 6 bear out such an assumption. Since this difference in pressure

TABLE 6.—*Changes in Pressure in Brain Tissue and in Cerebrospinal Fluid of Dogs After Intravenous Injection of Epinephrine Hydrochloride*

Date	Procedure	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg	Mean Blood Pressure, Mm. Hg
7/30/42	Before injection...	18	11	16	110
	Intravenous injection of 1 cc. of 1:1,000 solution of epinephrine hydrochloride.....	26	25	32	190
		18	5	8	110
8/ 7/42	Before injection				
	Open to exterior	0	6	10	110
	Injection of 2 cc. of 1:1,000 solution of epinephrine hydrochloride				
	Open to exterior	0	18	31	190
	Open to exterior	0	7	12	106
8/12/42	Before injection				
	Open to exterior	0	2	6	90
	Injection of 1 cc. of 1:1,000 solution of epinephrine hydrochloride				
	Open to exterior	0	6	10	170
	Open to exterior	0	4	6	80
7/ 6/42	Before injection				
	Open to exterior	0	..	6	120
	Injection of 1 cc. of 1:1,000 solution of epinephrine hydrochloride				
		..	..	18	150
		..	..	13	130

TABLE 7.—*Random Values for Cisternal, Intraventricular and Intracerebral Pressures* *

Date	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg
7/ 2/42	40	33	35
7/ 3/42	45	37	37
	135	97	97
7/ 6/42	50	40	41
7/ 7/42	36	26	26
7/11/42	26	20	22
7/13/42	26	19	19
7/18/42	15	10	11

* The differences here noted in the cisternal, the intraventricular and the intracerebral pressures are beyond the limits of experimental error.

between the two reservoirs of fluid depends most probably on the resistance the tissue lining the passageway between the two structures offers to the passage of fluid, the magnitude of the effect will vary from moment to moment, according to changes in volume in the tissues at the site of such resistance.

With water perfusion the pressure in the ventricles may rise to high levels above the cisternal pressure. If a small trephine hole is now made in the calvarium (the dura mater being left intact), the swollen brain is seen to lie taut against the calvarium, to the obliteration of the sulci and gyri. Here, then, a condition has been produced in which the reservoir of subarachnoid fluid has been all but depleted and the reservoir of fluid in the ventricles prevented from escaping the cranial cavity, as evidenced by the high intraventricular and the low cisternal pressure. Now any increase in the bulk of the brain consequent on vasomotor phenomena (active or passive dilatation) can no longer take place with small changes in pressure made

TABLE 8.—*Effect of Variation in Ether Concentration on Intracranial Pressures in Normal Dogs*

Date	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg	Change in Ether Concentration
9/ 5/41	..	..	25	
	..	..	25	
	..	..	26	Ether increased
	..	..	36	
	..	..	38	
	..	..	38	
	..	..	37	Ether decreased
	..	..	30	
	..	..	28	
8/31/42	8	2	3	
	9	4	6	
	8	8	15	Ether increased
	9	3	4	Ether decreased
	8	16	18	
	10	16	18	
7/18/42	6	5	5	
	6	2	3	Ether increased
	6	3	4	Ether decreased
	7	3	5	Ether increased
7/23/42	16	23	16	
	16	21	14	
	16	22	15	Ether increased
	16	23	18	
	19	25	20	
	20	24	22	
8/20/42	17	18	16	
	19	16	12	
	20	15	12	Ether decreased
	19	13	10	
	20	18	16	Ether increased
	24	20	19	
	25	14	13	Ether decreased
	24	..	13	Ether increased
	25	18	16	

possible by displacement of cerebrospinal fluid, but these phenomena (vascular) are limited in scope by the degree to which the brain stem itself can be displaced through the foramen magnum and by the large changes in pressure this entails. The rigidity of the cranial cavity to changes in volume of the brain under these conditions is substantiated by the following experimental data:

1. The pulse appearing in the meniscus of the devices for measurement of the intracerebral and the intraventricular pressures is much increased in amplitude over the normal. This is especially striking at the higher levels of pressure. The pulse does not appear in a normal

animal when the cisternal pressure is raised mechanically by means of a pressure bottle.

2. There now exists a close relation between the blood pressure and the intraventricular pressure. A rise in blood pressure is accompanied by a parallel rise in intraventricular pressure, and on the death of the animal the latter drops to near zero. If there is a small trephine hole in the calvarium, with the dura mater left intact, one may easily feel these changes in pressure in the tautness of the brain against the dura mater. Figure 1 illustrates this.

3. In normal dogs the effect of variation in the concentration of the ether anesthetic (a powerful cerebral vasodilator) on the intracerebral pressure was found to differ somewhat in different animals, the changes in intracerebral pressure in general being relatively small. The data in table

TABLE 9.—*Effect of Variation in Ether Concentration on Intracranial Pressures After Water Perfusion* *

Date	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg	Change in Ether Concentration
8/29/41	..	..	54	
	..	..	60	Ether increased
	..	..	110	
	..	..	122	
	..	..	130	Ether decreased
	..	..	90	
	..	..	70	
	..	..	54	
9/ 5/41	..	..	50	
	..	..	52	Ether increased
	..	..	94	
	..	..	70	
7/13/42	..	..	38	Ether increased
	..	..	70	
	..	..	41†	
8/27/42	23	84	43	Ether increased
	22	95	98	
9/ 2/42	38	45	38	Ether increased
	38	75	80	
	39	90	93	
9/10/42	15	42	47	
	18	49	55	Ether increased

* Readings were taken at two minute intervals.
† Animal dying.

8 show this. After a moderate amount of water is perfused, the intraventricular pressure is somewhat above the cisternal pressure. Some of the data obtained by an increase in the concentration of ether under these conditions were striking. Pronounced increases in pressure did not occur in every case, perhaps because a further increase in the concentration of ether did not cause much more dilatation. At very high levels of intracerebral and intraventricular pressure variation in the concentration of the anesthetic did not have much effect on these pressures. The data appearing in table 9 show the effect of an increase in concentration of ether when the intracerebral and intraventricular pressures are moderately high. They are much greater than those in the normal animal. In these animals, too, one may easily feel the changes in pressure with differences in ether concentration by the alteration in tautness of the cerebral hemispheres against the intact dura mater after a small trephine hole has been made in the calvarium.

4. After water perfusion, when the intraventricular pressure has risen somewhat above the cisternal pressure, intravenous injection of epinephrine, which gives rise to an increase in the systemic blood pressure through splanchnic constriction, now also produces large changes in intracerebral and intraventricular pressure. If a trephine hole is present in the calvarium, with the dura mater intact, one can again feel, and actually see, these changes in intracranial pressure in response to the systemic effects of epinephrine. In table 10 are listed the data on this observation; they may be compared with the data in table 6 for normal animals. In the normal animal the changes in intracerebral and intraventricular pressure are

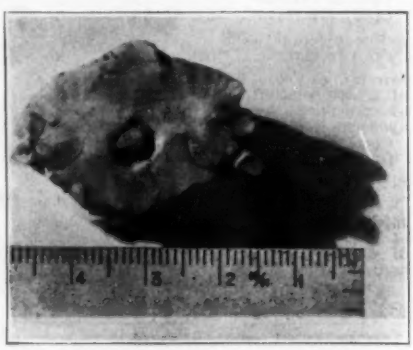

Fig 8.—Relationship of the anterior lobe of the vermis of the cerebellum to the floor of the fourth ventricle in normal dogs.

not nearly as pronounced as those in the experimental animal. It may be noted how independently the intracerebral and the intraventricular pressures vary from the cisternal pressure.

An understanding of the etiologic factors by which such a rigid state may be attained in the cranial cavity is of theoretic and practical importance.

1. A block between the ventricular system and the rest of the cerebrospinal spaces, together with an increase in the quantity of ventricular fluid, may cause this rigid intracranial state.

Experimental Demonstration.—In an animal which has been recently killed a small trephine hole is made in the subtemporal part of the calvarium, the dura mater being left intact. The muscles of the neck and the occipitoatlantal ligament are now cut through and the atlas is chipped away so that the brain stem is brought into view. If now a needle is inserted through the dura into the lateral ventricle and fluid is introduced under pressure, the hemispheres of the brain are forced

outward and become taut against the calvarium, with flattening of the gyri and obliteration of the sulci. At the same time the brain stem can be seen to herniate downward through the foramen magnum, the extent of the herniation varying directly with the degree of pressure transmitted to the ventricles. The expanding hemispheres, having displaced all the subarachnoid fluid, are prevented from further expansion by the calvarium, and the brain moves toward the one remaining opening in the cranium, the foramen magnum.

2. Given a block between the ventricles and the cisterna magna, an increase in the bulk of the brain due to edema will soon obliterate the subdural fluid spaces, and any further increase in cerebral bulk, not being accompanied by simultaneous displacement of ventricular fluid, will result in a large increase in pressure of the intracranial contents.

3. Severe cerebral edema, even without a block between the lateral ventricles and the cisterna magna, will lead to the same condition, as the brain tissue displaces all the intracranial fluid.

TABLE 10.—*Effect on Intracerebral and Intraventricular Pressures of Intravenous Injection of Ephinephrine Hydrochloride, After Production of Edema*

Date	Procedure	Cisternal Pressure, Mm. Hg	Intraventricular Pressure, Mm. Hg	Intracerebral Pressure, Mm. Hg	Mean Blood Pressure, Mm. Hg
8/ 9/41	Open to exterior....	0	..	44	80
		0	..	50	80
	Intravenous injection of 1 cc. of 1:1,000 solution of epinephrine hydrochloride				
		0	..	190	260
			..	146	240
		..	..	130	170
		..	..	50	76
		..	..	50	70
8/12/41	Intravenous injection of 1 cc. of 1:1,000 solution of epinephrine hydrochloride	30	..	76	120
		35	..	140	190
		32	..	90	140
		30	..	80	120
7/29/42	Open to exterior....	0	44	45	108
	Intravenous injection of 2 cc. of 1:1,000 solution of epinephrine hydrochloride	0	154	164	230
	Animal dies as blood pressure descends rapidly and respiration ceases.....	0	16	16	16 (at death)
8/6/42	Open to exterior....	0	..	45	125
	Intravenous injection of 1 cc. of 1:1,000 solution of epinephrine hydrochloride				
		..	..	135	180
		..	..	155	195
		..	..	30	100

The type of block created in the experiments here reported is interesting and instructive. Although fluid was prevented from leaving the lateral ventricles, passage of fluid from the cisterna magna into the lateral ventricles readily took place (page 515). The anatomic relations of the passageway between the ventricles and the cisterna magna suggest the reason for this valvelike action. The ventral portion of the cerebellum, including the central lobe, the lingula and the anterior medullary velum, is found to encroach to an appreciable extent on the space of the fourth ventricle in normal dogs (fig. 8). With water perfusion the vascularity of the cerebellum makes it subject to appreciable edema. This increase in bulk of the cerebellum acts in two ways to occlude completely the continuity of the fourth ventricle: (1) The cerebellum as a whole, because of the bony tentorium above, is displaced downward on the fourth ventricle, and (2) the increase in bulk of the central lobe causes it to become more firmly wedged into the fossa of the fourth ventricle. After water perfusion examination of the brains reveals both an increase in bulk of the central lobe of the cerebellum in relation to the fossa of the fourth ventricle and narrowing of the aperture of the aqueduct of Sylvius. Fluid coming in from the cisterna magna and exerting its pressure from beneath the obstructing lobe in the fossa of the fourth ventricle would tend to lift the lobe (or force the brain stem ventrad) and force passage into the lateral ventricle. On the other hand, fluid coming through the aqueduct of Sylvius and impinging on the obstructing lobe of the cerebellum higher up, rather than from beneath would have no tendency to relieve the obstruction and thus could not force passage. This hypothetic explanation may account for the valvelike character of the obstruction experimentally produced.

This type of block, in conjunction with an increase in the bulk of the brain and in the amount of ventricular fluid, accounts for the rigid condition produced in the water perfusion experiments. Weed and McKibben were the first to demonstrate that increased production of cerebrospinal fluid and increased brain bulk result from perfusion of water.[6]

COMMENT

The experimentally produced state of high intraventricular and low cisternal pressure gives rise to dire respiratory and circulatory effects, which disappear when the disparity between the two pressures is reduced. This indicates the danger involved in lumbar puncture when the possibility of a block between the ventricular reservoir and the subdural fluid spaces exists. In the presence of such a block the cisternal pressure is of no value in determination of the level

6. Weed, L. H., and McKibben, P. S.: Am. J. Physiol. **48**:512, 1919; footnote 2.

of intracerebral or intraventricular pressure. In cases of severe clinical concussion some evidence exists as to the presence of such internal hydrocephalus. Shapiro and Jackson [7] found that in persons who died as a result of severe cranial trauma there was dilatation of the lateral ventricles of the brain with increase in fluid (from a normal volume of 10 to 15 cc. to values of 30 to 60 cc.), which did not run freely into the subdural spaces. French clinicians [8] have also stressed the importance of traumatic internal hydrocephalus following severe cranial trauma. In cases of this complication lumbar puncture would constitute a danger to the patient's life, whereas ventricular puncture would be of definite value. Whether or not the type of block existing in such clinical material is similar to the one way type of block produced in these studies must await an experimental answer.

Experimentally observed and reported here is one of the consequences of high intraventricular and relatively low cisternal pressure, namely, herniation of the brain stem into the foramen magnum. It is quite possible that this herniation gives rise to the respiratory and circulatory effects observed. It is also possible that the consequent effects on respiration and blood pressure are due to herniation of the mesencephalon through the incisura tentorii consequent to a state of high intraventricular and low cisternal pressure.

The experiments in series 2 in which the intraventricular pressure was raised above the cisternal pressure constitute an incomplete study of the phenomena involved. The effects contingent on a slow increase in the intraventricular pressure over a long period need to be studied. Such a condition would be more like that resulting from water perfusion or slowly forming clinical hydrocephalus (internal) than the abrupt increase in the intraventricular pressure produced in these experiments.

Studies of vasomotor phenomena in the brain could be favorably pursued along the lines indicated in the section on intracranial mechanics. For this purpose a more accurate device for measurement of intracerebral pressure would be of great value.

SUMMARY AND CONCLUSIONS

Respiratory and Circulatory Effects.—In animals into which distilled water was perfused while the blood pressure, the cisternal pressure, the intraventricular and intracerebral pressures and the respiration were simultaneously recorded on the kymograph, with ether as the anesthetic, the intraventricular and the intracerebral pressure rose above the cisternal pressure. When the intraventricular pressure reached a level between 60 and 25 mm. of mercury below the diastolic blood pressure, circulatory and respiratory embarrassment developed.

The respiratory and circulatory embarrassment associated with high levels of intraventricular and intracerebral pressure could be relieved by ventricular drainage, which sharply lowered both the intraventricular and the intracerebral pressure.

No circulatory or respiratory embarrassment occurred when both the cisternal and the intraventricular pressure were at high levels, but medullary embarrassment appeared soon after the cisternal pressure was lowered, the intraventricular pressure alone remaining high.

After insult to the medullary centers consequent to states of high intraventricular and low cisternal pressure, these centers became embarrassed at lower levels of pressure.

In acute experiments on otherwise normal animals in which the intraventricular pressure was abruptly raised to levels between 60 and 10 mm. of mercury below the diastolic blood pressure while measures were taken to keep the cisternal pressure low, the respiration was most directly affected, becoming depressed and inhibited more quickly in general at the higher pressures than at the lower pressures employed.

The general tendency in these experiments was toward a distinct slowing in heart rate, the retardation being as a rule of greater magnitude the higher the intraventricular pressure. Individual differences tending toward recovery of rate to normal, and even to increase in rate above the normal controls, were noted.

The hemodynamic effects in these experiments were not constant, the general tendency being toward a decrease in the blood pressure. Individual variations in the opposite direction were noted.

The respiratory depression and the circulatory effects resulting from these abrupt increases in intraventricular pressure were eliminated by raising the cisternal pressure to the level of the intraventricular pressure or by lowering the intraventricular pressure.

The ill effects of increased intraventricular pressure (with low cisternal pressure) are due to herniation of the medulla into the foramen magnum. This herniation was experimentally observed in dogs consequent to elevation of the intraventricular pressure while the cisterna

7. Shapiro, P., and Jackson, H.: Swelling of Brain in Cases of Injury to Head, Arch. Surg. **38**:443 (March) 1939.

8. Denis, R.: J. de chir. **42**:873, 1933. Arnaud, M.: Bull. et mém. Soc. nat. de chir. **59**:843, 1933.

magna was opened to the exterior. The possibility also exists that the respiratory and circulatory effects were due to a herniation of the mesencephalon through the incisura tentorii.

The effects of high intraventricular and low cisternal pressure while the intraventricular pressure is more slowly raised over a prolonged period needs further investigation. Such a study would more closely simulate the conditions in the water perfusion experiments and in cases of clinical internal hydrocephalus.

Evidence incidentally gathered in the water perfusion experiments (but prior to the perfusion) suggests that adjustment to the reverse condition, namely, a high cisternal and a low intraventricular pressure, is more easily made by the medullary centers.

The fallacy of the cisternal pressure being regarded as a measure of the intraventricular and the intracerebral pressure when cerebral edema and/or the possibility of internal hydrocephalus exists receives emphasis from the results of the water perfusion experiments.

In view of the evidence of internal hydrocephalus consequent to severe cranial trauma in some cases, use of lumbar puncture as a means of relief of intracranial tension in such cases is invalid and contraindicated. Ventricular drainage is indicated for such a condition.

Ventricular drainage should be performed as quickly as possible because of the insult offered to the medullary centers by prolonged tension. Ventricular drainage, together with artificial respiration and administration of isotonic solution of three chlorides (infused into the central end of the common carotid artery), was efficacious in restoring respiration and increasing the blood pressure after severe medullary trauma in the water perfusion experiments.

Intracranial Mechanics.—In normal animals there exists a certain range within which the intraventricular pressure may differ from the cisternal pressure.

At any level to which the cisternal pressure may be raised, the increase in intracerebral pressure is contingent on the filling of the lateral ventricles and is close to the intraventricular pressure attained.

The pulse in the brain tissue and the lateral ventricles of normal animals is relatively small at all levels of pressure to which the cisternal and the intraventricular pressure may be raised. This was evidenced by the magnitude of fluctuations of the fluid meniscus in the devices for measuring the intracerebral and intraventricular pressures.

The intracerebral and intraventricular pressures of normal animals are relatively little affected by changes in the vascular volume of brain tissue brought about by increase in the concentration of ether (ether being a strong vasodilator of cerebral capillaries) or by systemic injections of epinephrine.

Changes in vascular volume of the brain may be compensated for chiefly by displacement of fluid from the cranial cavity, first from the subarachnoid spaces and then from the ventricles.

With water perfusion and its consequent cerebral edema the subarachnoid fluid is all but depleted, and the ventricular fluid becomes trapped in the ventricles.

Loss of most of the subdural and the ventricular fluid as a means of compensation for changes in vascular volume in the cranial cavity limits such changes to the extent to which the brain stem itself can herniate from the cranial cavity and the relatively large changes in pressure this entails.

This rigid condition in the cranial cavity manifests itself in (*a*) a relatively much larger pulse in the brain tissue and in the ventricles, especially after high pressure levels have been reached, than in the normal brain; (*b*) dependence to a large degree of the intraventricular and intracerebral pressures on the blood pressure, especially when high intracerebral and intraventricular pressures have been reached, the intracerebral and intraventricular pressures rising with the blood pressure and dropping to near zero levels at death, and (*c*) the relatively larger than normal changes in intracerebral and intraventricular pressure consequent to increasing concentration of ether or systemic injection of epinephrine.

The block created between the lateral ventricles and the cisterna magna in the water perfusion experiments was such as to allow fluid to pass from the cisterna magna to the lateral ventricles but not from the lateral ventricles to the cisterna magna.

Dr. Arno B. Luckhardt made many helpful suggestions during the course of the procedures here reported.

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SUPPRESSION OF MOTOR RESPONSE IN MAN

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In 1876 Ferrier [1] stated: "There is no reason to suppose that one part of the brain is excitable and another not. The question is, how the stimulation manifests itself." As one is prone to look for active responses, one may fail to observe other manifestations elicited by electrical stimulation of nerve tissue.

In 1845, biologic inhibition was first experimentally demonstrated by the Weber brothers,[2] who showed that vagal stimulation slowed the heart. For their studies a background of cardiac activity was necessary. Similarly, a background of activity is necessary for any studies of inhibition, whether central or peripheral. Setschenow [3] (1863) employed the "withdrawal" response of the frog's hindlimb as the background of activity for his attempts to localize inhibition within the central nervous system. Bubnoff and Heidenhain [4] (1881) showed that inhibition of a muscular contraction may be brought about through tactile stimulation of an ipsilateral member. Sherrington and his collaborators [5] demonstrated and defined reciprocal innervation, with its two component parts, excitation and reciprocal inhibition. They showed that the principles of summation, convergence, fractionation, recruitment and after-effects apply to inhibition as well as to excitation.

Inhibition, in the sense of a reduction of the background of motor activity, by electrical stimulation of the cerebral cortex has been observed by many investigators.[6] However, there appear to be several forms of inhibition. These require definition. One may consider muscular relaxation as a response to stimulation of the appropriate structure—cortical focus or peripheral sensory nerve. This may be inhibition in a reciprocal sense, or it may be something entirely different. If, in stimulating a focus of the cerebral cortex electrically, one varies the intervals between stimuli, one may fail to get the "typical" peripheral motor response for that area. Further, one may fail to elicit a motor response with a stimulus previously supramaximal because this stimulation followed a violent motor after-discharge. Finally, a previously electrically excitable cortical area may become inexcitable after stimulation of one of several particular areas of the cortex. These examples compel one to consider the following variables in particular when studying diminution or abolition of a

From the Department of Neurology and Neurological Surgery and the Illinois Neuropsychiatric Institute, University of Illinois College of Medicine.

1. Ferrier, D.: The Functions of the Brain, London, Smith Elder & Co., 1876, p. 130.

2. Weber, E. F., and Weber, E. H.: Experimenta, quibus probatur nervos vagos rotatione machina galvanomagneticae irritatos, mortum cordis retardare et adeo intercipere, Ann. univ. di med. (no. 347) **116**:227, 1845 (series 3, vol. 20).

3. Setschenow, J.: Physiologische Studien über die Hemmungsmechanismen für die Reflexthätigkeit des Rückenmarks im Gehirne des Frosches, Berlin, A. Hirschwald, 1863.

4. Bubnoff, N., and Heidenhain, R.: Ueber Erregnungs- und Hemmungsvorgänge innerhalb der motorischen Hirncentren, Arch. f. d. ges. Physiol. **26**:137, 1881.

5. Creed, R. S.; Denny-Brown, D.; Eccles, J. C.; Liddell, E. G. T., and Sherrington, C. S.: Reflex Activity of the Spinal Cord, New York, Oxford University Press, 1932. (*b*) Denny-Brown, D. E.: Selected Writings of Sir Charles Sherrington, New York, Paul B. Hoeber, Inc., 1940.

6. (*a*) Brown, T. G., and Sherrington, C. S.: On the Instability of a Cortical Point, Proc. Roy. Soc., London, s.B **85**:250, 1912. (*b*) Bubnoff and Heidenhain.[4] (*c*) Dusser de Barenne, J. G., and McCulloch, W. S.: Suppression of Motor Response upon Stimulation of Area 4s of the Cerebral Cortex, Am. J. Physiol. **126**:482, 1939; (*d*) Suppression of Motor Response Obtained from Area 4 by Stimulation of Area 4s, J. Neurophysiol. **4**:311, 1941. (*e*) Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: The "Motor" Cortex of the Chimpanzee, ibid. **4**:287, 1941. (*f*) Garol, H. W.: The "Motor" Cortex of the Cat, J. Neuropath. & Exper. Neurol. **1**:139, 1942. (*g*) Hines, M.: The "Motor" Cortex, Bull. Johns Hopkins Hosp. **60**:313, 1937. (*h*) Leyton, A. S. F., and Sherrington, C. S.: Observations on the Excitable Cortex of the Chimpanzee, Orang-Utan and Gorilla, Quart. J. Exper. Physiol. **11**:135, 1917. (*i*) Mettler, F. A.: Relation Between Pyramidal and Extrapyramidal Function, A. Research Nerv. & Ment. Dis., Proc. **21**:150, 1942. (*j*) Rioch, D. M., and Rosenblueth: Inhibition from the Cerebral Cortex, Am. J. Physiol. **113**:663, 1935. (*k*) Tower, S. S.: Extrapyramidal Action from the Cat's Cerebral Cortex: Motor and Inhibitory, Brain **59**:408, 1936.

peripheral motor response: (1) the preexisting background of peripheral motor activity; (2) the strength of the stimulus of threshold intensity for the given motor response; (3) the antecedent activity of the tissue stimulated; (4) the structure and connections of the parts stimulated; (5) the particular anesthetic employed, and (6) the source and distribution of the background of motor activity, particularly as affected by posture. It is on the basis of such variables that we make distinction for defining the terms used in this paper.

1. Extinction [7]—the state of diminished excitability due to induced antecedent neural activity. For example, electrical stimulation of a cortical focus for flexion of the knee evokes that response, but if, thirteen seconds later, one stimulates the same focus, no flexor response results, whereas if one stimulates that focus, say, two seconds after the first stimulation, there may be the counterpart of extinction, namely, facilitation, while stimulation, perhaps twenty-five seconds after the first stimulation, evokes only the usual response.

2. Neural "fatigue or exhaustion"—the state of failure of response to a previously adequate stimulus, delivered singly or in a volley, because of immediately preceding generalized neural overactivity, e. g., an unresponsive state following a motor after-discharge.

3. Inhibition—a state of restraint by an active secondary agent, i. e., in the sense that the response is forbidden, for example, reciprocal inhibition [5] of an antagonistic muscle during an active contraction of the agonist.

4. Suppression of motor response [8]—a particular form of inhibition: a state in which a strength of stimulus to a cortical focus previously adequate to provoke a peripheral motor response will not elicit such a response subsequent to stimulation of another cortical area known to induce such suppression, e. g., stimulation of arm area 4 subsequent to stimulation of area 4s. The latent period and the degree and the duration of restraint depend on the strength and the duration of the stimulus applied to the suppressor area and the time relations between the two specific stimuli.

The respective variations in the suppression of motor response, under the conditions of experimentation, depend mainly on the intensity and the duration of the stimulus. Thus, in the temporary or transient holding in abeyance of a peripheral motor after-discharge, the latent period is observably brief; the degree of restraint is complete in both agonist and antagonist, and immediately after removal of the stimulus the rhythmic alternating (clonic) movements resume only when the stimulus is of short duration and not intense enough to summate or undergo recruitment. That is, the effect may be only a fraction of what may be obtained with a more intense stimulus. In the suppression of existing muscular tension the same features obtain.

On the other hand, the raising of the threshold of a cortical "motor point" is dependent on a more prolonged or a more intense stimulus applied to a suppressor area. Under such circumstances there are summation and recruitment of other suppressor or inhibitory neurons; i. e., a greater fraction of the suppressor mechanism has been called into play. In each instance the duration of the suppressor effect varies before there is a return of the former electrical excitability of the cortical focus known to provoke peripheral motor responses, and this time interval will depend on the duration and intensity of the stimulation of the suppressor area. This phenomenon is not to be confused with suppression of spontaneous cortical electrical activity, as shown by the electrocorticogram, the mechanism of which is known to require neural continuity between the cortical suppressor area, the nucleus caudatus and the thalamus.[9] On the other hand, suppression of peripheral motor response has been demonstrated after large lesions in the nucleus caudatus, the putamen, the globus pallidus and the substantia nigra and after complete removal of the cerebellum,[6d] an observation indicating that such structures are not necessary for the suppression of motor responses by cortical stimulation.

Dusser de Barenne and his collaborators [10] described the suppression of motor response in the monkey (Macaca mulatta) and the chimpanzee (Pan satyrus) by electrical stimulation of regions homologous to Brodmann's [11] cyto-

7. Dusser de Barenne, J. G., and McCulloch, W. S.: Factors for Facilitation and Extinction in the Central Nervous System, J. Neurophysiol. **2**:319, 1939.

8. Dusser de Barenne and McCulloch (footnotes 6*c* and *d*). Dusser de Barenne, Garol and McCulloch.[6e]

9. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Physiological Neuronography of the Cortico-Striatal Connections (Monkey), A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:246, 1942.

10. Dusser de Barenne, J. G., and McCulloch, W. S.: Functional Organization in the Sensory Cortex of the Monkey (Macaca Mulatta), J. Neurophysiol. **1**:69, 1938; footnote 6*c* and *d*. Drusser de Barenne, Garol and McCulloch.[6e]

11. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, J. A. Barth, 1909.

architectonic areas 8, 2 and 19, and recently area 24.[12] These authors called these areas 8s, 2s, etc. In addition, there is area 4s, which forms a narrow band between Brodmann's area 4 and area 6 (Hines[6g]). The characteristic responses obtained from electrical stimulation of such suppressor areas,[13] varying somewhat with the duration and intensity of stimulation, are as follows: (1) a lessening of existing muscular tension throughout the body, particularly on the contralateral side; (2) a pronounced rise in

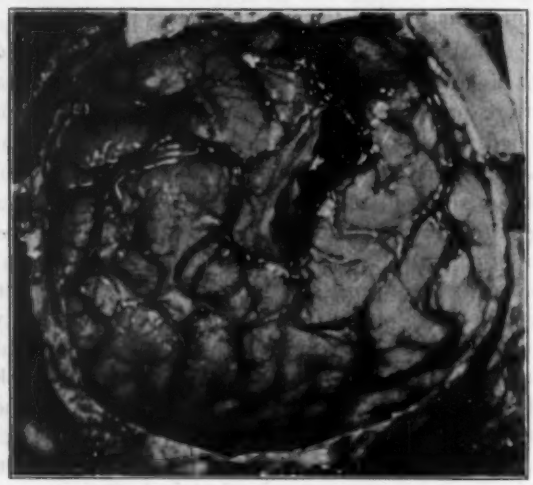

Fig. 1.—Photograph of the cerebral cortex exposed at operation after the posterior half of the precentral gyrus in the "arm" and "leg" areas had been removed. The region of extirpation appears black. The suppressor area was located in the curve of the large cortical vein lying anterior to the lower part of the extirpation.

threshold to electrical stimulation of area 4; (3) a holding in abeyance of a motor after-discharge induced by stimulation of area 4; (4) a failure to produce, in the absence of summation or recruitment, a peripheral motor response, and (5) a return of normal electrical excitability following suppression. These phenomena are abolished by undercutting of the area, e. g., area 4s.

It is on the basis of the aforementioned characteristics that we report, for the first time in man, the occurrence of suppression of motor response, induced through electrical stimulation of a specific cortical area immediately anterior to the precentral gyrus.

12. Bailey, P.; von Bonin, G.; Davis, E. W.; Garol, H. W.; McCulloch, W. S.; Roseman, E., and Silveira, A.: Functional Organization of the Medial Aspect of the Primate Cortex, J. Neurophysiol. **7**:51 (Jan.) 1944.

13. Dusser de Barenne and McCulloch.[6d] Dusser de Barenne, Garol and McCulloch.[6e]

REPORT OF A CASE

P. de F., aged 24, was referred by Dr. Daniel H. Levinthal, of Chicago. While he was under ether anesthesia the central segment of the cortex of his left cerebral hemisphere was exposed, on Aug. 3, 1943. He had been troubled by a persistent tremor on his right side, and an operation was contemplated for relief of this condition. At the close of the operation the posterior half of the left precentral gyrus, in the "arm" and "leg" regions, was removed down to the bottom of the central fissure (fig. 1). This procedure completely abolished the tremor. This aspect of the case will not be dealt with further here.

The depth of anesthesia was decreased, and a systematic electrical stimulation of the exposed cerebral cortex was made, with a 60 cycle sine wave stimulator, designed by Dr. T. J. Case, and bipolar silver–silver chloride electrodes, with an interelectrodal distance of 3 mm. Observers noted and recorded the responses to the cortical stimulation. Dr. Percival Bailey made a sketch of the cortical foci stimulated and recorded the responses following electrical stimulation (fig. 2).

Responses to Stimulation.—1. Electrical bipolar stimulation of the precentral gyrus, near the fissure of Rolando, at a threshold of 1.6 volts, evoked a peripheral motor response in the leg, the arm and the face (fig. 2). Repeated stimulation failed to disclose any appreciable variation in threshold in any of these regions.

2. After generalized muscular spasticity had developed from lightening of the anesthesia, stimulation of the suppressor region (*9* in figure 2) was followed by immediate relaxation of the existing muscular tension in the contralateral arm (the right leg and the left extremities were not manipulated, since the operative position was not suitable). This observation was repeated a number of times and was observed by us and by several other persons, including Dr. Bailey.

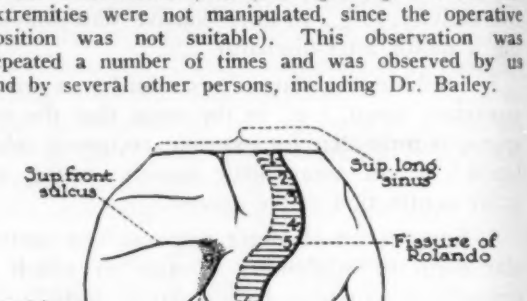

Fig. 2.—Artist's elaboration of a sketch of the cerebral cortex exposed at operation. The insert indicates the general relation of the exposed cerebral cortex. The numbers designate areas of various responses to electrical stimulation. The area for flexion of the right hip is indicated by *1*; for contraction of the right quadriceps femoris muscle, by *2*; for contraction of the right pectoralis major muscle, by *3*; for flexion of the fingers of the right hand, by *4*; for flexion of the right elbow and wrist, by *5*; for movement of the neck and right shoulder, by *6*; for movement of the right corner of the mouth and contraction of the right platysma myoides muscle, by *7*; for movement of the lower lip on the right side, by *8*, and for the suppressor area—areas 4s, by *9*. The area which was extirpated has been indicated by cross hatching.

3. After stimulation of the suppressor region (*9* in figure 2), the threshold in the posterior part of the precentral gyrus became notably increased over what it had been previously. The elevated threshold remained, for variable periods, somewhat dependent on the intensity and duration of the stimulus to the suppressor region (*9* in figure 2).

4. When the intensity of the stimulus was increased to 2.5 volts and the electrodes maintained in contact with the posterior part of the precentral gyrus (leg, arm or face region of area 4γ), a motor after-discharge was evoked in the corresponding peripheral member. Then the immediate stimulation of the suppressor region (*9* in figure 2) was followed, after a definite latent period, estimated to be about five to ten seconds, by an abrupt cessation of the motor after-discharge, whereas it gradually stopped if the suppressor area was not stimulated. This abolition of motor after-discharge was always elicited from this suppressor area (*9* in figure 2), and never from any other area of the exposed cortex.

5. Other suppressor regions, such as areas 2, 8 and 19, were not stimulated.

COMMENT

The suppression of motor response in the monkey and the chimpanzee has been adequately discussed by Dusser de Barenne and his collaborators. The phenomenon has never before been described in man, though it has, reportedly, been sought.

The extent of the suppressor area in our patient was not determined. It was comparable in position and response to area 4s in the macaque [14] or to band III in the chimpanzee cortex [15] and appeared to be part of the strip which von Bonin [16] designated, on microscopic evidence, as area 4s in the human brain.

In the cat, Rioch and Rosenblueth,[6j] using a background of peripheral motor responses produced by cortical electrical stimulation, found that the lowest threshold for "inhibition" was obtained from Langworthy's point *A* on the cat's cortex.[17] Stimulation of this point *A* ipsilaterally or contralaterally produced "inhibition" in chronic and acutely decerebellated preparations. The effect was most pronounced on the same side. In further attempts to localize the "inhibitory" tract or tracts in the spinal cord, electrical stimulation of point *A* ipsilaterally or contralaterally after hemisection of the cord still yielded bilateral "inhibition." This effect obtained whether the hemisection was dorsal or lateral, and was produced even when only one anterior quadrant of the cord remained intact. The authors concluded that the mode of mediation of inhibition in the cat was probably by means of the direct pyramidal tract and perhaps involved internuncials to the motoneurons.

Tower [6k] investigated various areas of the cat's cortex before and after transection of the pyramids in acute and chronic preparations. Her observations (employing 60 cycle current) disclosed areas of the cortex stimulation of which consistently yielded "relaxation of muscular tone" and "inhibition" of spontaneous or cortically induced movements and stopped cortically induced motor after-discharge. The area corresponding to Langworthy's point *A* was found to elicit these responses readily. Tower cited the Vogts (1919), who observed that rhythmic mastication, induced electrically via their cortical area 6bβ (monkey), was "denervated" or inhibited by stimulation of their cortical area 8 γ. The regions described by Tower for the cat correspond fairly closely with those described by one of us (Garol [6f]) on the basis of cortical electrical stimulation and physiologic neuronographic studies of the functional organization of the cat's cortex. Tower's contribution indicates that the pyramidal tracts are probably not the means of mediation of these "inhibitory" phenomena, as Rioch and Rosenblueth thought probable.

Further important studies on the primates are the investigations of Hines [6g] and of Dusser de Barenne and associates. Hines, employing a 60 cycle current to delimit the anterior border of the electroexcitable cortex for discrete movements, found that this corresponded closely to the cytoarchitectonic area 4 (Macaca mulatta). Electrical stimulation anterior to this border frequently produced "inhibition of tonic extension." Subsequent ablation of this narrow cortical "strip" between area 4 and area 6 resulted in peripheral somatic manifestations differing from those induced by ablation of either area 4 or area 6. "Release" phenomena, such as muscular spasticity, clonus and brisk irradiating tendon reflexes, were obtained after removal of this strip between area 4 and area 6. Unilateral ablation produced these changes transiently, while bilateral ablation produced them permanently. This picture was quite different from that obtained by section of the pyramidal decussation, as a result of which no such release phenomena were exhibited and the muscles became

14. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Functional Organization of Sensory and Adjacent Cortex of the Monkey, J. Neurophysiol. **4**:324, 1941.

15. Bailey, P.; Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Sensory Cortex of Chimpanzee, J. Neurophysiol. **3**:469, 1940.

16. von Bonin, G.: Architecture of the Precentral Motor Cortex and Some Adjacent Areas, in Bucy, P. C.: The Precentral Motor Cortex, Urbana, Ill., University of Illinois Press, to be published.

17. Langworthy, O. R.: The Area Frontalis of the Cerebral Cortex of the Cat, Its Minute Structure and Physiological Evidence of Its Control of the Postural Reflex, Bull. Johns Hopkins Hosp. **42**:20, 1928.

hypotonic. Electrical excitation of area gigantocellularis after section of the pyramids elicited nonsomatotopic, complex patterns of movement —in contrast to the somatotopic, discrete movements obtained when the pyramids were intact.

Dusser de Barenne and McCulloch [6e] while studying the functional organization of the cerebral cortex in the macaque and, further, while investigating the factors for facilitation and extinction, described in the monkey the occurrence of suppression of motor response from stimulation of a narrow band (area 4s) of frontal cortex at the junction of area 4 and area 6. Stimulation of this area was found to suppress, after a relatively long latent period, the repetition of extension of the wrist induced electrically from a cortical focus in area 4. If they avoided stimulating area 4s, no alteration in response was forthcoming, save under particular conditions, when "extinction" [7] would become manifest. This experiment was repeated with various muscle groups, and the same phenomenon occurred. With other collaborators, they subsequently found the phenomenon on electrical stimulation of cortical areas 8, 2, 19 and 24, as well as area 4s, in the macaque and in the chimpanzee. Somewhat similar areas were observed in the cat.[6f]

It was shown by Dusser de Barenne and his collaborators that local topical applications of a solution of strychnine sulfate or strychnine nitrate to any one of these suppressor areas produced another phenomenon, namely, suppression of spontaneous electrical activity, i. e., an isoelectric state, transient in nature, affecting various component areas of the cortex in sequence and not appearing to be of somatotopic character. The latter phenomenon was studied and found to concern, as necessary and apparently sufficient, the nucleus caudatus, the thalamus and the cerebral cortex.[9] In contrast, we have already noted that these structures alone are not necessary for the suppression of motor response.

Electrical stimulation of the basal ganglia, especially the nucleus caudatus, evokes a relaxation of muscular tension, as reported by Mettler.[61] Further studies must be conducted to determine the mechanism involved in the suppression of motor response and any possible relation of the corpus striatum to that phenomenon.

The existence of corticostriatal projection systems has not been proved by histologic study. The latest report was made by Glees.[18] With a new staining technic, he noted degeneration of the fine unmyelinated nerve fibers in the nucleus caudatus after removal of cortical areas of the cat known to produce suppression of motor response on electrical stimulation, or suppression of spontaneous electrical activity on topical application of strychnine to the cortex.

CONCLUSIONS

Suppression of motor response was elicited by electrical stimulation of a circumscribed area of the human cerebral cortex.

The area involved lies just anterior to the precentral gyrus and inferior to the posterior part of the superior frontal sulcus. The entire extent of the area was not determined.

This area is considered homologous to area 4s in the macaque and in the chimpanzee.

The entire neural mechanism concerned in this phenomenon is not known.

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18. Glees, P.: Personal communication to W. S. McCulloch, 1943.

ABSCESS WITHIN THE SPINAL CORD

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

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Abscess of the spinal cord is by no means as common as is abscess of the brain. This is evident from a survey of the cases in the literature and the fact that most textbooks of neurology omit the subject entirely or mention it only briefly in passing. Abscess of the spinal cord is not, however, an unknown or a new disease entity. A careful search through the literature revealed that probably the first description of this condition was published as early as 1830.[1] Since that time 39, or possibly 40, reports[2] have appeared (table 1). In 1926 Woltman and Adson[3] summarized the data in 29 cases which had been described in the literature and added 1 case of their own. Since then, 9 other cases have been reported.

CLASSIFICATION

Abscesses involving the spinal cord may be conveniently classified according to location. They may be outside the dura (epidural), beneath the dura but outside the substance of the cord (subdural or extramedullary intradural) or within the substance of the cord itself (intramedullary). The discussion in this communication will be limited to abscesses of the intramedullary type. Abscesses of the spinal cord may also be classified as single or multiple, macroscopic or microscopic or encapsulated or nonencapsulated.

ETIOLOGIC CONSIDERATIONS

Like its cerebral counterpart, an abscess of the spinal cord may develop by metastasis from some distant focus or by contiguity (i. e., from an infection in the vertebral column or nearby tissues), or the abscess may be primary, i. e., without an apparent or a demonstrable preexisting focus of infection (table 2). In 16 of the cases reported in the literature the abscess developed by contiguous extension. In 15 of these cases the abscess was single and in 1 case multiple. In 6 instances a single abscess developed without evidence of meningitis, the lesion occurring after or in conjunction with fracture of the spine in 3 cases, with Pott's disease in 1 case, with perinephritic abscess in 1 case and with carcinoma of the spine in 1 case. Meningitis was present in 7 of the 15 cases of single abscess. In these cases an abscess followed fracture of the spine (1 case), nevus (1 case), Pott's disease (1 case), meningocele (1 case), paravertebral abscess (1 case), spina bifida (1 case) and boils on the buttocks (1 case). In 2 cases a single abscess developed after a suppurative process in the middle ear. In each of these cases the brain was involved, as well as the meninges. In the only reported instance of multiple abscess developing by spread from a nearby focus (Pott's disease) the meninges were not involved.

In 5 instances multiple abscess was reported to be of metastatic origin. The abscesses occurred as a sequel to endocarditis in 1 case, to urethritis in 1 case and to bronchiectasis in 3 cases. In 1 of the 5 cases (that of endocarditis) there were no other pathologic changes in the central nervous system. Meningitis was a complicating factor in the case of urethritis. In 1 case of bronchiectasis there was a pathologic process in the brain, in addition to involvement of the spinal cord, and in the other 2 cases meningitis was present, as well as involvement of the brain and spinal cord. In 11 instances a single abscess was reported to have developed by metastasis. In these cases the single abscess occurred as a sequel to, or during the course of, empyema, gangrene of the lung, infection of the lung of unspecified cause, endocarditis, prostatic abscess, septic abortion, infection of the hand, actinomycosis and fracture of the foot. In 2 of these cases (endocarditis and actinomycosis) the meninges were not involved; in 2 cases (empyema and infection of the lung) there was simul-

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1. Hart, J.: Case of Encysted Abscess in the Centre of the Spinal Cord, Dublin Hosp. Rep. **5**:522-524, 1830; cited by Woltman and Adson.[3]

2. Forster: Zur Pathologie und Klinik der ventral sitzenden Rückenmarkgeschwülste, Zentralbl. f. d. ges. Neurol. u. Psychiat. **44**:712, 1926.

3. Woltman, H. W., and Adson, A. W.: Abscess of the Spinal Cord: Report of a Case with Functional Recovery After Operation, Brain **49**:193-206, 1926.

TABLE 1.—*Data on Cases of Abscess of the Spinal Cord Reported in the Literature*

	Age, Yr.	Sex	Primary Focus	Location, Segment of Cord	Type of Abscess	Organism	Outcome
Hart [1]	75	?	Primary in cord	D1-D12	Single	.....	Death
Ollivier, C. P.: De la moëlle et de ses maladies, Paris, Méquignon-Marvis & fils, 1837, vol. 1, p. 291; cited by Woltman and Adson [3]	23	M	Fracture vertebra C7	C7-D8	Single	.....	Death
	60	M	Fracture vertebra D10	D10	Single	.....	Death
Fairbrother: M. Times & Gaz. **5**: 190, 1852	69	M	Primary in cord	D8	Single	.....	Death
Jaccoud, S.: Études de pathogénie et de semiotique; Les paraplégies et l'ataxie du mouvement, Paris, Delahaye, 1861; cited by Woltman and Adson [3]	32	M	Primary in cord	D6 down	Single	.....	Death
Demme, R.: Klinische Mittheilungen aus dem Gebiete der Kinderheilkunde; Medicinische Berichte über die Tätigkeit des Jenner'schen Kinderspitales in Bern im Laufe des Jahres 1875, Berne, 1876; cited by Woltman and Adson [3]	3½	F	Primary in cord	Lumbar	Multiple	.....	Death
Feinberg: Berl. klin. Wchnschr. **13**: 463-465, 1876; cited by Woltman and Adson [3]	60	M	Fracture vertebra L1	L1 down	Single	.....	Death
Nothnagel, H.: Wien. med. Bl. **7**: 287-290, 1884	?	M	Bronchiectasis	D5 down	Multiple	.....	Death
Dubreuilh, W.: Bull. Soc. d'anat. et physiol. norm. et de path. de Bordeaux **8**: 13-26, 1877; J. de méd. de Bordeaux **16**: 352-356, 1886-1887	2½	F	Nevus, C6-C7	Medulla to lumbar region	Single	.....	Death
Uhlmann, O.: Ztschr. f. klin. Med. **16**: 39-55, 1899	27	M	Gonococcic urethritis	C and L	Multiple	.....	Death
Eisenlohr, C.: Deutsche med. Wchnschr. **18**: 111-113, 1892	43	M	Empyema	Pons, medulla and cervical region	Single	Short bacteria	Death
Schlesinger, H.: Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. a. d. Wien. Univ. 1894, no. 2, pp. 114-136	28	F	Prostatic abscess	Medulla to D4	Single	Staphylococcus	Death
Homén, E. A.: Rev. neurol. **3**: 97-102, 1895	56	M	Bronchiectasis	C4 to D8	Multiple	Streptococcus	Death
Skala, J. A.: Časop. lék. česk. **35**: 213-216, 1896; cited by Woltman and Adson [3]	22	M	Gangrene of lung	Upper dorsal	Single	.....	Death
Schlesinger, H.: Deutsche Ztschr. f. Nervenh. **10**: 410-418, 1897	28	F	Pott's disease	L and S	Single	Staphylococcus	Death
Cavazzani [21]	18	F	Fracture vertebra D12	D12	Single	.....	Laminectomy; recovery but persisting paraplegia
Chiari, H.: Ztschr. f. Heilk. **1**: 351-372, 1900	43	M	Bronchiectasis	C and D	Multiple	Pneumococcus and actinomyces	Death
Silfvast, J.: Deutsche Ztschr. f. Nervenh. **20**: 94-102, 1901	30	M	Apical infection	C4 to D2	Single	.....	Death
Pribitkoff, G. I., and Malolietkoff, S. L.: J. nevropat. i psikhiat. **1**: 85-102, 1901	30	F	Actinomycosis	D2 down	Single	.....	Death
Cassirer [24]	?	F	Endocarditis	C, D and L	Multiple	.....	Death
Turner, W. A., and Collier, J.: Brain **27**: 199-208, 1904	61	F	Carcinoma of spine	C8-D1	Single	Staphylococcus and streptococcus	Death
	37	F	Pott's disease	C3-C8	Multiple	.....	Death
	17	M	Pott's disease	C6-D7	Single	.....	Death
Wolff, A.: Virchows Arch. f. path. Anat. **198**: 545-553, 1909	8 days	M	Meningocele	D7-L4	Single	.....	Death
Kawashima, K.: Virchows Arch. f. path. Anat. **200**: 461-487, 1910	35	M	Primary in cord	D to L	Single	.....	Death
	42	M	Primary in cord	D and L	Multiple	Streptococcus; gram-negative bacteria	Death
Hitchcock, C. W.: J. A. M. A. **68**: 1318-1319 (May 5) 1917	?	M	Infection of hand	D to S	Single	Staphylococcus	Laminectomy; death
Lesné and Belloir: Ann. de méd. **12**: 329-336, 1922	44	M	Actinomycosis	D	Single	Actinomyces	Death
Moersch, F. P.: Arch. Neurol. & Psychiat. **7**: 745-752 (June) 1922	25	M	Actinomycosis	C to S	Single	Actinomyces	Death
Woltman and Adson [3]	11	F	Primary in cord	D6-D8	Single	Staphylococcus	Laminectomy with recovery
Schmitz, C.: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **116**: 68-70, 1926	37	M	Infection of middle ear	?	Single	Streptococcus	Death
Nonne, M.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **13**: 574-579, 1925-1926	11	M	Infection of middle ear	D4-D6	Single	Streptococcus	Laminectomy; death
Sittig, O.: Ztschr. f. d. ges. Neurol. u. Psychiat. **107**: 146-151, 1927	25	F	Septic abortion	D4-D7	Single	Staphylococcus	Laminectomy; death
Barnes, F. L.: New England J. Med. **203**: 725-727, 1930	18	M	Boils on buttocks	D7 to cauda	Single	Staphylococcus	Death
Abeshouse, B. S., and Bogorad, D. B.: Urol. & Cutan. Rev. **39**: 295-301, 1935	3½	F	Perinephritic abscess	D4-D5	Single	.....	Laminectomy; death
Urechia, C. I.: Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 809-811, 1935	47	M	Paravertebral abscess	Filum	Single	.....	Drainage; death
Walker and Dyke [22]	3	F	Spina bifida	L3-L5	Single	Pneumococcus and coliform bacilli	Laminectomy with recovery
Altenburger [25]	30	F	Endocarditis	D7	Single	Staphylococcus	Laminectomy; death
Alessi and Fasiani [23]	28	M	Fracture of right foot	D7-D9	Single	Staphylococcus, streptococcus, pneumococcus, actinomyces	Laminectomy and drainage with recovery

taneous involvement of the brain without evidence of meningitis; in 1 case (prostatic abscess) there were involvement of the brain and meningitis, and in 6 cases (gangrene of the lung, septic abortion, infected hand, fracture of the foot and actinomycosis, 2 cases) the meninges were involved.

Of the cases in which the origin was unknown or the abscess could be considered primary, the lesion was single in 5 and multiple in 2. Of the cases of single abscess, no other pathologic changes in the central nervous system were reported in 3, and lesions in the brain and meninges occurred in 2. Meningitis was present in 1 of the cases of multiple abscess and was absent in the other.

The reports in the literature on abscess of the cord are too few to permit the formulation of any hard and fast rules regarding the cause.

TABLE 2.—*Causes of Abscess of the Spinal Cord*

Primary Focus	Single Abscesses	Multiple Abscesses	Total Number of Cases
Direct extension	..	..	16
Fractured vertebra	4	..	
Pott's disease	2	1	
Nevus	1	..	
Carcinoma of vertebra	1	..	
Meningocele	1	..	
Paravertebral abscess	1	..	
Spina bifida	1	..	
Perinephritic abscess	1	..	
Boils on buttocks	1	..	
Infection of middle ear	2	..	
Metastatic spread	..	..	16
Bronchiectasis	..	3	
Empyema	1	..	
Gangrene of lung	1	..	
Endocarditis	1	1	
Urethritis	..	1	
Prostatic abscess	1	..	
Septic abortion	1	..	
Infected hand	1	..	
Actinomycosis	3	..	
Fracture of foot	1	..	
Infection of lung	1	..	
Primary in cord	5	2	7

The age of incidence, as pointed out by Woltman and Adson,[3] varied from eight days to seventy-five years. The condition was more frequent in males than in females (25 males, 13 females and 1 whose sex was not reported). The greatest incidence (65 per cent) in males occurred between the ages of 20 and 50, while in 33 per cent of the females the condition occurred before the age of 5 years and in 58 per cent between the ages of 10 and 40 years.

The organisms most commonly encountered were staphylococci and streptococci. Pneumococcus, Actinomyces, Diplococcus and Bacillus coli were reported less frequently. In only 20 cases was the presence of organisms reported, whether in the blood, the spinal fluid or the pus from the abscess. In many of the cases more than one organism was identified.

The organisms producing an abscess may reach the cord by various routes. The infection may be carried by the arteries or the veins from a distant focus or by the lymphatics from nearby or distant foci. Because of the important role played by the vascular and lymphatic systems in the production of abscess of the cord, a survey of these systems is appropriate. The anterior spinal artery, which is single throughout its course, is formed by convergence of branches from each of the vertebral arteries, one branch arising from each artery. These branches are given off at an acute angle. The anterior spinal artery, besides originating from the vertebral arteries and receiving branches from them, also derives branches from the cervical branch of the inferior thyroid artery and the intercostal, lumbar, iliolumbar and lateral sacral arteries.[4] The posterior spinal arteries are also branches of the vertebral arteries. Generally, they do not unite, as do their homologues on the anterior surface of the cord, but continue a separate course downward along the posterior lateral sulcus and terminate at the lower cervical level. The direction of flow of blood in the anterior spinal artery and the posterior spinal arteries is downward. The posterior spinal arteries for the remainder of their course are continuations of the lowermost lateral branches of the terminal portion of the anterior spinal artery, and the direction of the flow of blood is upward.[5] A rich arterial plexus of delicate vessels, the vasocorona, surrounds the spinal cord and is, for the most part, an anastomosis between the anterior and the posterior spinal arteries.[6] The terminal vessels (intramedullary) of the vasocorona are of small caliber and originate from this plexus at right angles. These intramedullary vessels are freely branching immediately after entering the cord, and they supply the white matter, a narrow marginal zone of the gray matter in the anterior horns and most of the gray matter of the posterior horns. The sulcocommissural artery, derived solely from the anterior spinal artery, ends in a rich terminal ramification within the substance of the cord and supplies the remainder of the structure.

The intramedullary veins leave the cord and drain into three dorsal and three ventral venous channels, which anastomose freely and finally drain into the vertebral, the intercostal, the lumbar and the lateral sacral veins. The vertebral

4. Mettler, F. A.: The Spinal Cord and Its Surrounding Media, in Neuroanatomy, St. Louis, C. V. Mosby Company, 1942, chap. 1.

5. Bolton, B.: The Blood Supply of the Human Spinal Cord, J. Neurol. & Psychiat. **2**:137-148, 1939.

6. Bing, R., and Haymaker, W.: Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord, ed. 11, St. Louis, C. V. Mosby Company, 1940, pp. 28-29.

veins have a great number of connections with the veins of the abdominal and thoracic walls, the azygos system of veins and the veins of the pelvic viscera. Batson [7] stated that the vertebral veins serve as storage lakes, as well as a system for drainage, and that because of the low pressure in the veins, stagnation is frequent. Coughing and straining tend to produce stasis in, or even a backward flow into, these channels, so that it is possible for organisms from a distant focus to reach the cord, with possible abscess formation.

According to Weil,[8] the cord may become infected through the lymphatics. Strictly speaking, there are no lymphatics in the spinal cord.[9] The lymph is carried in the adventitial lymph spaces of Virchow and Robin, which are around the blood vessels, and drain into the larger intrapial lymph spaces. Galkin [10] injected india ink into the spinal subarachnoid space at various levels of the cord and noted the intensity of staining of the lymph vessels and nodes remotely located from the cord. His experiments showed connections between the subarachnoid space and the lymphatics of the mediastinum, the abdominal cavity and the retroperitoneal region via the lymphatics along the spinal nerves. In cases of abscess formation following disease processes of the vertebrae or the surrounding tissues, the organism probably reaches the cord along these channels, either with or without the production of generalized meningitis. It is not difficult to imagine the progress of an infection into the substance of the cord via these channels without producing at least a localized meningeal reaction, such as occurs in the brain.

The mechanism of production of metastatic abscess was studied by Hoche.[11] In an interesting group of experiments, he introduced aseptic emboli (pollen, dust or clay or air) into the aortas of various animals; after killing the animals, he observed infarcts in the spinal cord, provided the emboli were small enough to enter the intramedullary vessels. He also injected various organisms into the circulation but noted that abscesses were rarely formed in the cord. With the introduction, however, of emboli and organisms simultaneously, or with the introduction of septic emboli into the aorta, he observed that abscess of the spinal cord was a common occurrence. Hanna,[12] in his analysis of cases of metastatic abscesses of the brain, concluded that abscess was a sequel to septic embolism or infection of a previously formed area of infarction. The same condition would undoubtedly hold true for abscess formation in the spinal cord.

The reasons for the comparative rarity of abscesses of the spinal cord are purely conjectural. Elsberg [13] stated that in all probability the relatively small mass of the cord, as compared with that of the brain (2:100), is responsible in part for the infrequency of abscess formation in the cord, while Woltman and Adson mentioned, in addition to this factor, the possibility that some protective agent in the cord, probably chemical, and the protected location of the cord, have something to do with the rarity of abscesses in this structure. It is not inconceivable that the delicacy of the intramedullary vessels and the angle of origin of the anterior and posterior spinal arteries function as a protection against septic emboli reaching the cord.

Other factors which undoubtedly are at least partially responsible for the rarity with which abscess of the spinal cord is reported are the infrequency of postmortem examinations of the spinal cord in cases in which abscesses are most likely to be present and the comparatively small number of sections studied when the cord is removed. DeJong,[14] in his analysis of 68 cases with an incontrovertible diagnosis of subacute bacterial endocarditis, noted involvement of the central nervous system in 17. The primary disorders present in this series included meningoencephalitis, subarachnoid hemorrhage and congestion and edema of the brain, the presence of all these conditions being confirmed at autopsy. The author made no mention of examination of the spinal cord in any of his cases. Rosenow and Brown,[15] in a review of 144 cases of septicemia, and Kernohan, Woltman and Barnes,[16]

7. Batson, O. V.: The Functions of the Vertebral Veins and Their Role in the Spread of Metastases, Ann. Surg. **112**:138-149, 1941.

8. Weil, A.: Textbook of Neuropathology, Philadelphia, Lea & Febiger, 1933, chap. 8.

9. Tilney, F., and Riley, H. A.: The Forms and Functions of the Central Nervous System, ed. 3, New York, Paul B. Hoeber, Inc., 1938, chap. 8, pp. 111-118.

10. Galkin, W. S.: Zur Methodik der Injektion des Lymphsystems vom Subarachnoidalraum aus, Ztschr. f. d. ges. exper. Med. **74**:482-489, 1930.

11. Hoche, A.: Experimentelle Beiträge zur Pathologie des Rückenmarkes, Arch. f. Psychiat. **32**:209-250 and 975-1008, 1899; cited by Woltman and Adson.[3]

12. Hanna, R.: Cerebral Abscess and Paradoxic Embolism Associated with Congenital Heart Disease, Am. J. Dis. Child. **62**:555-567 (Sept.) 1941.

13. Elsberg, C. A.: Surgical Diseases of the Spinal Cord, Membranes and Nerve Roots, New York, Paul B. Hoeber, Inc., 1941, chap. 6, pp. 185-207.

14. DeJong, R. N.: Central Nervous System Complications in Subacute Bacterial Endocarditis, J. Nerv. & Ment. Dis. **85**:397-410, 1937.

15. Rosenow, E. C., Jr., and Brown, A. E.: Septicemia: A Review of Cases, 1934-1936 Inclusive, Proc. Staff Meet., Mayo Clin. **13**:89-93, 1938.

16. Kernohan, J. W.; Woltman, H. W., and Barnes, A. R.: Involvement of the Nervous System Associated with Endocarditis, Arch. Neurol. & Psychiat. **42**:789-809 (Nov.) 1939.

in a study of involvement of the central nervous system in cases of rheumatic, subacute bacterial and acute infective bacterial endocarditis, likewise made no mention of examination of the spinal cord. Blumer,[17] in a review of 300 cases of subacute bacterial endocarditis, noted involvement of the central nervous system in about 25 per cent, while Krinsky and Merritt [18] observed neurologic manifestations in 31 per cent of their series of cases of subacute bacterial endocarditis. Neither Blumer nor Krinsky and Merritt made mention of examination of the spinal cord at autopsy. Winkelman and Eckel,[19] in their study of changes in the brain associated with bacterial endocarditis, reported only 1 case of involvement of the spinal cord. In this particular instance no abscess was observed, but the histologic changes present in the cord corresponded to those in the brain. One instance in which similar lesions occur in the brain and in the cord is not sufficient evidence that the cord is always involved simultaneously and similarly in any pathologic condition of the brain. It calls to mind, however, the possibility of this occurrence, especially with disseminated lesions of the brain, such as may occur in association with generalized bacteremia. In 10 (25 per cent) of the cases of abscess of the spinal cord recorded in the literature and in 2 of the cases (2 and 3) reported in this paper, the pathologic processes observed in the brain and in the spinal cord were similar.

PATHOLOGIC FEATURES

The histologic picture in the cord varies a great deal, the features depending primarily on whether there is more than one abscess. The size and age of the abscess also determine the picture. In the cases encountered in the literature, the extent of the lesion varied from microscopic dimensions to involvement of the entire length of the cord by a single abscess. Many abscesses were reported as the size of a pea or a bean, while some involved several segments of the cord. A few of the larger lesions were partially encapsulated, while some, particularly those studied soon after the onset of symptoms, had no limitations whatever and could probably be classified as purulent myelitis with central softening and necrosis.

A review of the pathologic changes reported in the literature does not indicate any special preference for the location of the abscess, from the standpoint either of the level in the cord or of the columns involved. In the instances of spread of the infection by contiguity the cord was generally involved at a level corresponding to that of the initial lesion. In the cases of metastatic spread the upper half of the cord was involved more frequently than the lower half.

The histologic picture of the larger single abscess varies according to the stage in which it is seen, and it is identical with its counterpart in the brain. In a fully formed abscess the central core of pus and necrotic material is surrounded by a capsule of three distinct layers. The inner layer, surrounding the central cavity, is composed of a meshwork of collagenous fibers. Between the fibers one is usually able to see degenerated polymorphonuclear leukocytes and other, more poorly defined, cells. This layer, to all practical intents and purposes, is avascular. The middle layer is made up of newly formed capillary buds, histiocytes, polyblasts, fibroblasts and plasma cells. Compound granular bodies containing lipid particles may also be present, especially in the older lesions. The cells are all large and exhibit many transitional forms. The external, or third, layer is composed of connective tissue fibers, in the meshes of which are numerous cells, chiefly clasmatocytes and fibroblasts. Around the blood vessels, in particular, plasma cells and polyblasts are encountered. Thus it can be seen that the defense mechanism against an abscess is not so much a glial as a connective tissue reaction.[20]

The miliary abscesses, which vary greatly in size, appear microscopically as small nodules. These nodules, or clumps of cells, are composed of monocytes, lymphocytes, polymorphonuclear leukocytes and endothelioid cells. The nodules are generally scattered throughout the gray and the white substance of the cord, and many may be seen spreading from, or in close proximity to, a small vessel. This localization near a vessel is most likely the result of obstruction of a small blood vessel or capillary, with subsequent invasion of the infarcted or necrotic area by organisms. The organisms may at times be seen, both in the abscess and/or the vessel leading to the abscess. The endothelium of the vessels is usually swollen, and the capillaries are often hyperemic and prominent, but generally the vessel has no perivascular cuffing. Areas of hemorrhage frequently surround the small nodules. Many of the ganglion cells in the area are de-

17. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105-170, 1923.

18. Krinsky, C. M., and Merritt, H. H.: Neurologic Manifestations of Subacute Bacterial Endocarditis, New England J. Med. **218**:563-566, 1938.

19. Winkelman, N. W., and Eckel, J. L.: The Brain in Bacterial Endocarditis, Arch. Neurol. & Psychiat. **23**:1161-1182, 1930.

20. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, ed. 1, Baltimore, William Wood & Company, 1933, chap. 12, pp. 233-236.

stroyed and disappear, while those remaining in relation to the lesion show various stages of acute involvement. They are swollen and vacuolated and may be invaded by neuronophages.

Generally there is an increase of the glial cells throughout the cord, especially in relation to the lesion, and often the glial reaction is most noticeable at the periphery. The meninges may be thickened and the subarachnoid space invaded by inflammatory cells. In 22 of the cases which have been reported there was evidence of meningitis.

The changes in the cord may be attributed not only to the reaction of the tissue against the invading micro-organisms but to the reaction against the toxins liberated by the organisms.

SYMPTOMS

It is not always possbile to establish a characteristic symptom complex, since the symptoms of abscess of the cord vary from case to case. In some instances symptoms referable to the spinal cord may be entirely absent, while in others they are characteristic of either partial or complete transverse myelitis. The resulting signs depend on the location of the lesion within the cord, the size of the abscess, the number of abscesses and the amount of surrounding tissue involved. The symptoms of the underlying disease process, as well as those of complications in locations other than the spinal cord, may often mask the signs of involvement of the cord. This is especially true in small disseminated lesions of the cord when the brain is also involved, in contradistinction to a large single abscess within the spinal cord.

The reported data on the spinal fluid are inconclusive from a diagnostic standpoint but may be valuable at times. In a few instances organisms were noted. The pressures ranged from zero to 28 mm. of mercury. In a few instances a complete block was demonstrated and the fluid was xanthochromic. The number of cells present ranged from within normal limits to several thousand. The colloidal gold reactions varied from case to case, but in the majority a normal reaction was reported.

Generally, because of the underlying causes, the temperature records are valueless from the standpoint of diagnosis. Involvement of the spinal cord may be ushered in, however, by a sudden rise in temperature. The leukocyte count is generally of little value. In most instances, because of the primary cause of the abscess, leukocytosis is present before the cord is involved. A secondary increase in the number of white cells may occur at the time the cord is implicated.

PROGNOSIS AND TREATMENT

The prognosis of an abscess of the spinal cord is universally poor. It is of course influenced greatly by the severity of the underlying disease process responsible for the abscess, as well as the general resistance of the patient to the added infection. Four reports have appeared in the literature (Cavazzani,[21] Woltman and Adson,[8] Walker and Dyke[22] and Alessi and Fasiani[23]) in which the condition was stated to have been successfully treated. In Cavazzani's case, the patient lived but had a paraplegia which did not clear up. In each instance the cord was involved by a single abscess, and the treatment was laminectomy and/or drainage. In 6 instances, in spite of surgical intervention, the outcome was fatal. In no case was recovery reported to have followed involvement by multiple abscesses. There is a chance, however, that an abscess, recognized as such and treated early by surgical means, will in some instances respond favorably. No mention has been made in the literature of the use of sulfonamide compounds, either alone or in conjunction with drainage. It is reasonable to assume that with early spinal drainage and the early use of one of these compounds the course of an abscess might be influenced favorably.

REPORT OF CASES

CASE 1.—*History.*—A. T. T., a female infant aged 14 months, was admitted to the Jewish Hospital (Philadelphia), service of Dr. Arthur Dannenberg, on Aug. 11, 1939, because of fever and "hoarseness" in the chest. The birth and early development had been normal. At the age of 6 months the patient had the croup, and a few weeks prior to the present illness she had had chickenpox. The family history was irrelevant. Two days prior to admission, the infant appeared restless and cried a good deal. The mother also reported that the child had a fever, although the temperature was not recorded.

Examination.—On admission, the temperature, pulse rate and respiratory rate were recorded as 101.4 F. and 160 and 40 per minute respectively. There was no clinical evidence of pneumonia. The heart was normal clinically. There were several large purpuric spots on the feet and chest. Neurologic examination revealed moderate nuchal rigidity and absence of the abdominal reflexes and of the Kernig and Brudzinski signs. The spinal fluid contained 200 cells per cubic millimeter, 75 per cent of which were polymorphonuclear leukocytes. Cultures of the fluid were sterile. The temperature rose to 104.4 F., and sulfapyridine was administered, with a prompt fall in the temperature to 101 F. On August 14 the temperature rose to 104.2 F. The nuchal rigidity increased, and the child

21. Cavazzani, G.: Ascesso centrale traumatico del midallo spinale operato e guarito, Riv. ven. di sc. med. **30**:481-493, 1899.

22. Walker, R. M., and Dyke, S. C.: Abscess of the Spinal Cord, Lancet **1**:1413-1414, 1936.

23. Alessi, D., and Fasiani, G. M.: Der metastatische Rückenmarksabscess: Klinisch-chirurgischer Beitrag, Arch. f. Psychiat. **111**:695-706, 1940.

maintained a position of mild opisthotonos, with moderate extension of the right arm and leg and flexion of the left arm and leg. All the extremities were hypertonic. The reflexes on the right side were exaggerated; those on the left side were absent, and the Kernig and Brudzinski signs were positive. The blood dorsal region, which was available for examination showed no gross changes.

Microscopic examination of the cord revealed marginal gliosis. Sections showed evidence of considerable meningeal irritation but no actual meningitis. There was uniform gliosis throughout the cord, affecting equally both the white and the gray matter. The vessels were of increased prominence, but no inflammatory elements were present in the perivascular spaces. The motor cells of the ventral horns were decreased in number, and those that remained showed evidence of acute changes. The cells in Clarke's column were less involved. Within the ventral horn particularly, but also in the white matter (fig. 1 *A*) and in Clarke's

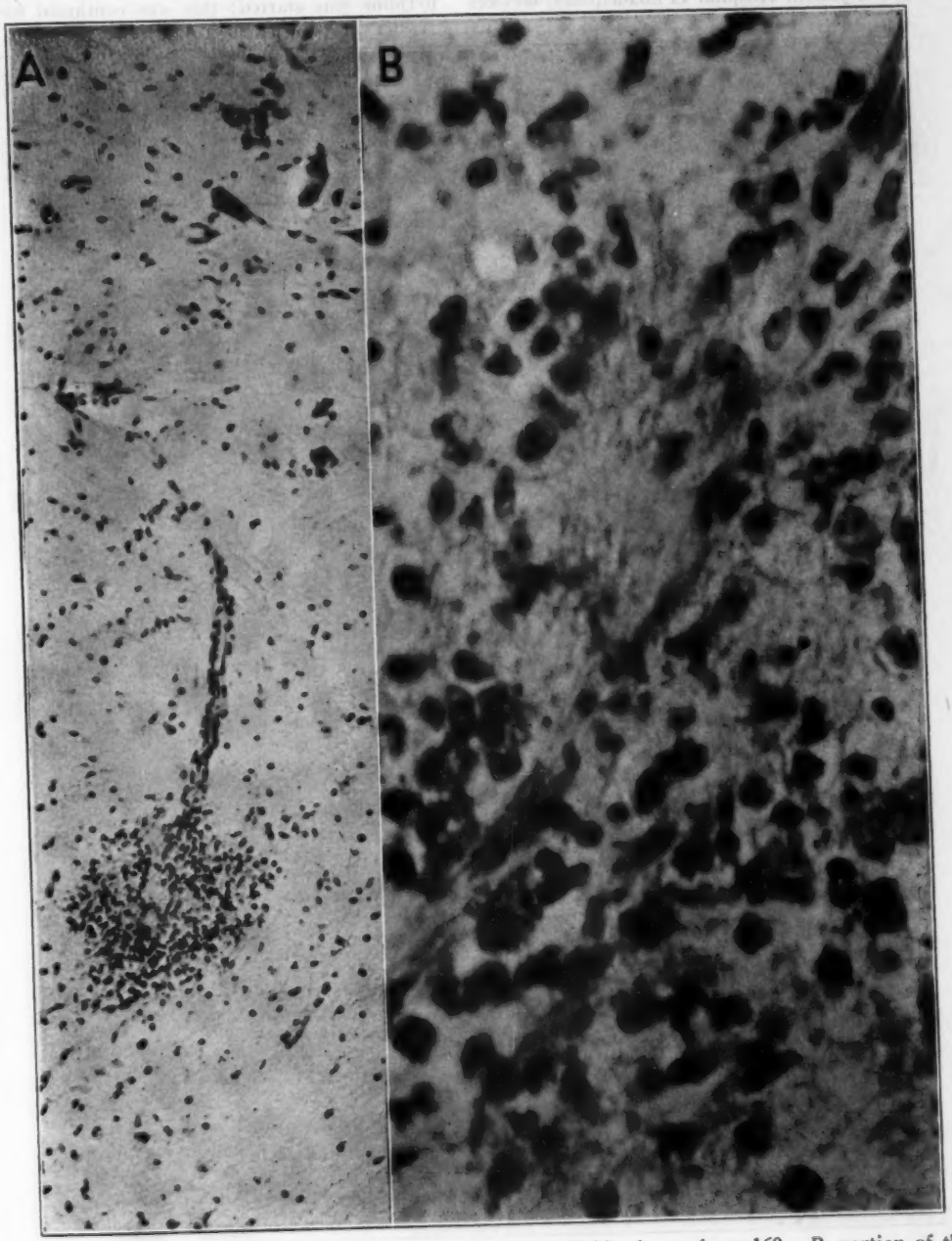

Fig. 1 (case 1).—*A*, abscess seen in close proximity to a small blood vessel; × 160. *B*, portion of the section shown in *A*; × 1,000. Toluidine blue stain.

culture showed Staphylococcus aureus, and culture of the spinal fluid was sterile.

Course.—The child's condition became progressively worse, and she died on August 16.

Necropsy.—The diagnosis was bacterial endocarditis (mitral valve), septicemia and multiple infarcts of the right kidney. The brain was not examined. The small portion of the spinal cord, probably from the

column (fig. 2 *A*), were several small abscesses, which were seen to be spreading from a central vessel. Within the abscesses, and also contained within some of the cells, were small clumps of organisms, resembling staphylococci (figs. 1 *B* and 2 *B*).

CASE 2.—*History.*—H. D., a man aged 46, was admitted to the Jewish Hospital (Philadelphia), services of Dr. Mitchell Bernstein and Dr. Joseph C. Doane, on Dec. 29, 1939, with a history of malaise and attacks of chills and fever every evening for six weeks prior to hospitalization. The family history was irrelevant. The patient gave no history of rheumatic fever.

Examination.—The right pupil was irregular. The teeth were carious. A loud systolic murmur was heard over the entire precordium; there were clubbing of the fingers and a small hemorrhage under one finger nail. The Wassermann reaction of the blood was 4 plus and that of the spinal fluid was negative. Culture of the blood yielded Streptococcus viridans. The temperature was 105 F. Treatment with sulfapyridine was started; this was continued for ten days and then discontinued because the temperature became normal. During the afebrile period the patient's blood culture was sterile, and the Wassermann reaction of the blood was reported as negative. On February 8 the blood culture was again positive for Strep. viridans; the temperature rose to 105 F., and sulfapyridine was again administered, with a prompt fall in temperature.

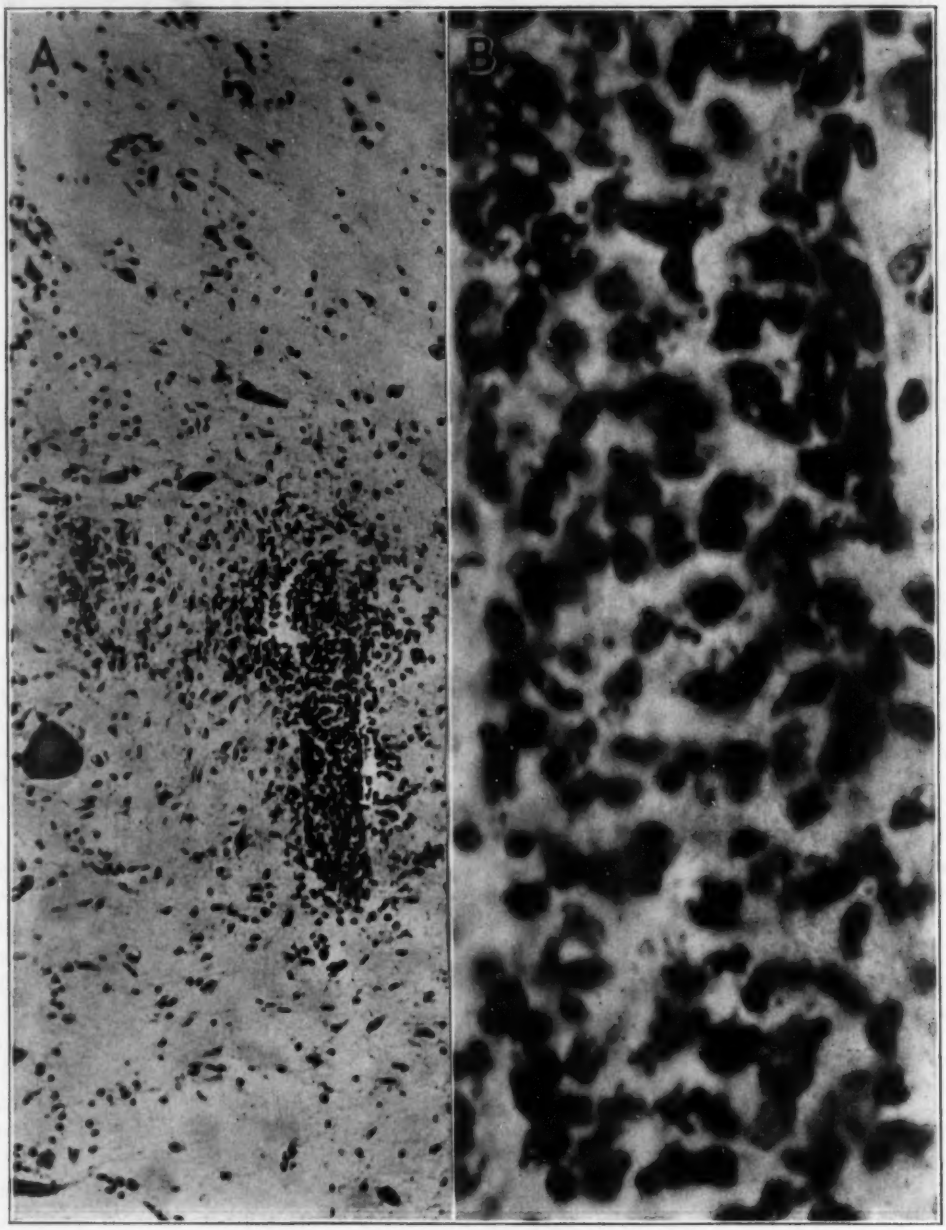

Fig. 2 (case 1).—*A*, abscess originating from a vessel in Clarke's column; × 160. *B*, portion of the field shown in *A*; × 1,000. Toluidine blue stain.

On February 22 the patient began to complain of dull, generalized abdominal pain, vertigo, nausea and vomiting. The next day he was listless; the pupils were still irregular and unequal (the left being slightly dilated); the eyes turned to the left, and spontaneous nystagmus was present. The patellar reflex was hyperactive on the left side, and the patient was incontinent.

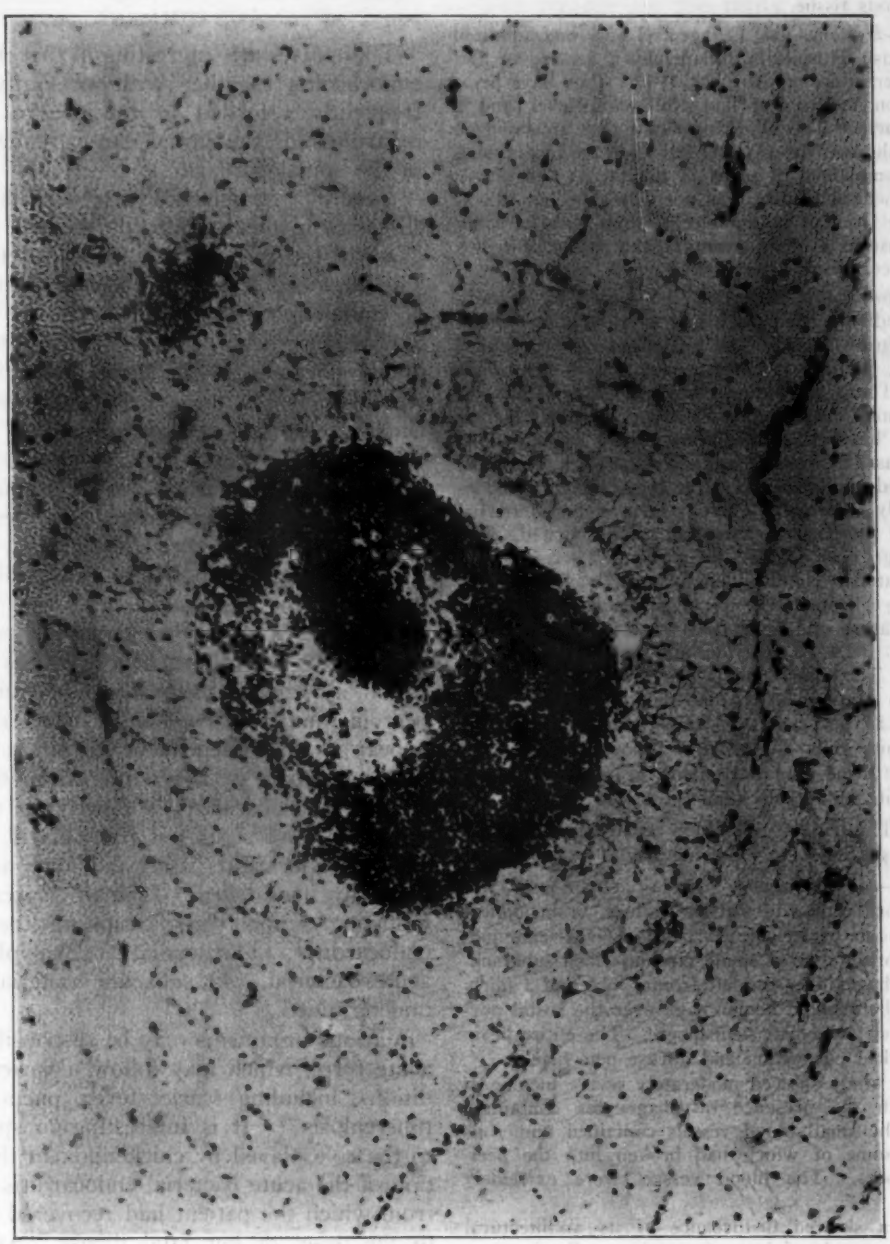

Fig. 3 (case 2).—Large and small abscesses in close proximity, with swollen and congested vessels. Toluidine blue stain; × 140.

Course.—The patient's condition became worse rapidly, and he died the following day.

Necropsy.—Examination revealed subacute bacterial endocarditis of the mitral and aortic valves, acute ulcerative endocarditis of the mitral valve and old rheumatic stenosis of the mitral and aortic valves. The brain showed hemorrhagic degeneration of the right cerebellar hemisphere; diffusely scattered, metastatic petechiae throughout the brain, the brain stem and the cord, and early atherosclerosis of the circle of Willis.

Diffusely and irregularly scattered throughout the cortex, the subcortex, the subcortical ganglia, the pons, the medulla and the spinal cord (fig. 3) were numerous metastatic abscesses. These varied greatly in size and were usually related to the small vessels. The cellular components of these abscesses were, in their order of frequency: monocytes, transitional lymphocytes, lymphocytes, polymorphonuclear leukocytes and endothelioid cells. Around many of these abscesses were areas of hemorrhage. The meninges showed moderate invasion of the subarachnoid space with inflammatory cells. In addition to these cellular elements there were fibroblasts and many phagocytes, some of which were filled

with pigment. There were generalized gliosis and softenings in many areas, with the concomitant glial reaction. The area of hemorrhagic degeneration in the cerebellum showed widespread destruction by discrete and diffuse invasion of inflammatory elements, similar to those previously described. There were also considerable hemorrhage and softening of the invaded and the contiguous tissue.

CASE 3.—*History.*—M. E., aged 63 (?), was admitted to the Jewish Hospital (Philadelphia), service of Dr. Mitchell Bernstein, on Aug. 22, 1940. Two days prior to admission the patient had chills and fever and a slight headache. The following day a rash appeared on her body; she was drowsy and later became incontinent. She also complained of pains in the thighs and pelvis. The past medical history was not available, but it was known that she had been under a physician's care for years because of a heart condition, the nature of which was not ascertained.

Examination.—On admission the patient was semicomatose and responded sluggishly to stimulation. There was a diffuse macular and punctate rash over the entire body, but it was more pronounced on the thighs and legs. There was dulness on percussion of base of the right lung, and crepitant rales were present in that area. The heart was fibrillating rapidly. The blood pressure was 155 systolic and 70 diastolic. The liver was enlarged and tender, and the inguinal lymph nodes were slightly enlarged. There was pronounced nuchal rigidity, but the Kernig sign could not be elicited. The Babinski sign was positive bilaterally. There was no ankle or patellar clonus. The patient was unable to open her eyes completely or to protrude her tongue. The temperature and pulse and respiratory rates were recorded as 102.4 F. and 115 and 28 per minute respectively. The spinal fluid was clear and colorless and under a pressure of 80 mm. of water. The hemoglobin was 85 per cent; red cells numbered 4,500,000 and the white cells 8,000, with a normal differential count. The urine contained many granular casts and red and white blood cells and a trace of albumin.

Course.—The patient's condition became progressively worse, and she died the following day.

Necropsy.—The diagnosis made at autopsy was auricular fibrillation with cardiac failure, bronchopneumonia and acute bacterial endocarditis. Gross examination of the brain showed small, circumscribed subarachnoid hemorrhages over the left frontal lobe and a fairly extensive subarachnoid hemorrhage over the rostal portion of the left cerebellar hemisphere. The entire brain showed marked congestion and diffuse petechiae.

Histologic study showed moderately severe meningeal fibrosis, with the presence of phagocytes containing pigment. The small blood vessels contained numerous monocytes, some of which had broken into the perivascular spaces. The blood vessels were extremely congested.

The cortex showed disturbance of its architectural layers as the result of loss of ganglion cells, increase of glia and edema. The small vessels were prominent as the result of proliferation and swelling of their lining cells. The medium-sized vessels showed mild thickening and hyalinization. Within the cortex were a few foci consisting of accumulations of cells with small groups of bacteria, representing small preabscesses. The subcortex showed an increase of glia, with numerous hyalinized vessels, which contained in their perivascular spaces phagocytes filled with pigment. Occasional, widely scattered, minute abscesses, as well as larger abscesses, were seen.

It is interesting that the basis pontis and the tegmentum also showed numerous abscesses. The cerebellum was apparently free.

The spinal cord presented a similar picture, with occasional abscesses scattered throughout both the gray and the white substance. The meninges also exhibited evidences of mild irritation.

COMMENT

These cases are interesting in that they present endocarditis together with an entity which is frequently recorded in the medical literature, regardless of the initial cause, namely, abscess of the spinal cord.

Cassirer [24] reported a case in which multiple abscesses in the cervical, dorsal and lumbar regions of the cord were a sequel to endocarditis. The abscesses were said to have been the result of emboli from the involved valves. Syringomyelia was also present in the cervical and dorsal portions of the cord, but no abscesses were observed in the syringomyelic area. Organisms were not isolated in this case.

Altenburger [25] reported a case of a single abscess in the seventh dorsal segment of the spinal cord which followed acute endocarditis and septicemia in the puerperium. Staphylococcus aureus haemolyticus was isolated from the pus of the abscess.

A discussion of the symptom complex of endocarditis is not the purpose of this communication. In general, however, one must always bear in mind that endocarditis does not usually appear as an independent entity but is more commonly part of a general infectious process. It is often obscured by overlying conditions, symptoms and signs not particularly characteristic of endocarditis itself and may, as a result, be easily overlooked. Libman [26] presented the following simple classification of the types of endocarditis: (1) rheumatic, (2) syphilitic, (3) acute bacterial, (4) subacute bacterial and (5) undetermined.

Various organisms may be responsible for the acute form, which may follow a variety of conditions, including scarlet fever, pneumonia and tuberculosis.[19] It is interesting to speculate as to the role played by chickenpox in the production of the acute bacterial endocarditis in case 1, from which the patient had recovered just prior to the onset of her fatal illness. Another interesting speculation is whether the changes in the spinal cord were secondary to the endo-

24. Cassirer, R.: Ueber metastatische Abscesse im Centralnervensystem, Arch. f. Psychiat. **36**:153-206. 1903.

25. Altenburger, H.: Rückenmarksabscess, Nervenarzt **10**:96, 1937.

26. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813-818 (March 24) 1923.

carditis or were the result of the generalized septicemia. In this case it is entirely likely that the cord would have been involved without the presence of the endocarditis, especially in view of the fact that the endocarditis was not clinically apparent. Lack of clinical evidence of endocarditis, however, does not exclude the heart entirely for at least some responsibility in the changes present in the cord.

Subacute bacterial endocarditis develops only in the presence of previously existing valvular lesions. This condition was fulfilled in case 2, in which there was an old rheumatic stenosis of the mitral and aortic valves, in addition to the acute changes on the valves. It is interesting to note that a history of rheumatic fever was lacking in this case. The patient, when admitted to the hospital, was not aware of any preexisting heart disease. It is reasonable to assume that the changes in the cord and brain were the result of emboli from the valves of the heart. Injury to the vessel walls must undoubtedly take place to allow passage of bacteria into the substance of the brain and cord. Such damage would also explain the hemorrhagic areas and the areas of softening which were seen microscopically.

In case 3 there was widespread and rapid involvement of the central nervous system and other organs of the body. The neurologic signs were general and inconclusive from the clinical standpoint and were undoubtedly masked by the underlying pathologic processes in the heart and lungs. This case illustrates the ease with which the involvement of the spinal cord could have been overlooked had not the cord been examined at necropsy.

SUMMARY

Abscess of the spinal cord may be single or multiple, large or small, and may involve any part or level of the cord. Staphylococci or streptococci are the usual causative organisms.

The reasons for the rarity of involvement of the cord are open to speculation. The delicacy of the intramedullary vessels, the acute angle of origin of the vessels supplying the cord, the infrequency of examination of specimens of the spinal cord and the comparatively small number of sections studied and the relatively small mass of the cord in comparison with the mass of the brain are all factors that must be taken into account.

The symptoms and signs vary according to the location and extent of destruction, both in the cord and in other parts of the central nervous system.

The histologic picture of an abscess of the cord is the same as that of an abscess in any other part of the central nervous system and varies according to the size and the age of the lesion. Organisms are frequently seen in and around the abscess.

The prognosis of an abscess of the spinal cord is poor. Occasionally, when the cord is involved by a single lesion, drainage may prove beneficial.

Dr. N. W. Winkelman, director of the John L. Eckel Laboratory of Neuropathology and professor of neuropathology in the University of Pennsylvania graduate school of medicine, permitted the report of these cases and gave advice and constructive criticism in the preparation of the paper.

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PSYCHIC DEAFNESS IN CHILDREN

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PRELIMINARY DEFINITION

Although the concept of "psychic deafness in children" was introduced into medicine by S. Heller (Vienna) more than half a century ago, Ewing [1] was right in complaining that almost no consideration had been given it in the literature.[2] It may therefore be well to discuss first the meaning of the term. "Psychic deafness in children" seems to indicate that there are youngsters in whom a trait, and only that trait, is responsible for their lack of any response to acoustic stimuli. In other words, the deafness of such children is not due to a pathologic condition of any part of the hearing organs—that is, in the external auditory meatus, the middle ear, the acoustic nerve or the acoustic center. The neurologist as well as the otologist, might be reminded by this definition of "hysterical deafness" as it appears in persons who suddenly lose their previously normal hearing after certain types of psychic shock. But, as will be shown later in this article, any identification of the pathologic process in the condition under discussion here with the lesion concerned in "hysterical deafness" is wrong, at least in general. The modern concept of "hysterical deafness" is based on the assumption of a subconscious struggle between wishes and desires, on the one hand, and reality, on the other, this struggle resulting in behavior similar to, or identical with, that of organically deaf persons. But this explanation does not seem to me to suffice for an understanding of psychic deafness in the majority of children so afflicted. At the end of this article I shall endeavor to prove the validity of this opinion and I shall propose the replacement of the term "psychic deafness in children" by another that seems to me to indicate better the underlying pathologic condition.

TESTS FOR ACUITY OF HEARING IN INFANTS AND IN CHILDREN SUSPECTED OF BEING DEAF OR HARD OF HEARING

The audiometric test is generally the method of choice at present. There are two exceptions to this rule: The test is not applicable to children under 5 years of age, and extreme hardness of hearing frequently seems to prevent even older children from giving reliable responses. With respect to the very young children, Westlake,[3] from his own experience, concluded:

> Children of three and four years of age show less consistency in their responses to the pure-tone-tests and show a wider deviation from the accepted normal threshold than older ones do, but these are very probably due to other factors than auditory acuity.

The second exception to the applicability of the method is based on my own experience that many children who were deaf according to the results of audiometric tests heard many sounds when tested by the method which I shall describe. The instrument used in the test is the accordion of Victor Urbantschitsch. It consists of a bellows, like that of an ordinary accordion, but has no keyboard. A hole to which whistles can be adjusted is cut into the frame of the bellows. Forty-two whistles, forming a scale of six octaves, ranging from G-1 to f-4, were furnished by the manufacturer. Originally the instrument was used chiefly to discover the distance at which the patient could hear the different pitches. I have recommended to otologists the method of "direct tone introduction" into the external auditory meatus. For this purpose, one end of a rubber tube is inserted by means of an ear olive into the meatus, while the other end touches the whistle from which the tone escapes. In this way the tone enters the ear directly, and experience has proved that if the patient hears the tone, some kind of reflex will result. The reflex may consist of blinking, withdrawal of the head from the olive or even jerking movements of the eyeballs.[4] Since all these movements are reflex, the method does not depend on the deliberate collaboration of the person examined. Therein lies the advantage that makes the method preferable to the audiometric test for small children and generally for older children who are hard of hearing. The audiometric test obviously

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1. Ewing, A. W. G.: Aphasia in Children, London, Oxford University Press, 1930.

2. Case 7 reported by Ewing seems to belong under the head of psychic deafness in children, although the author did not come to this decision.

3. Westlake, H.: Hearing Acuity in Young Children, J. Speech Disorders **7**:7-14 (March) 1942.

4. These movements have been described by me in the following paper: Ueber einen durch Schallreiz ausgelösten Augenmuskelreflex bei hochgradig Schwerhörigen, Ztschr. f. Hals-, Nasen- u. Ohrenh. **26**:511-520, 1930.

requires the strictest attentiveness of the patient, as well as his readiness to cooperate with the examiner, neither of which can be expected in youngsters. To older hard-of-hearing children, many of the tone stimuli of the audiometer are entirely unfamiliar because they have never, or seldom, received acoustic stimuli in their everyday lives. Therefore they may not understand what the examiner is asking them and consequently may not respond to the stimuli offered them by the audiometer.

Before I invented the method of "direct tone introduction," my diagnosis was based on examination with tuning forks and with the accordion of Urbantschitsch, so that hearing was measured only for distance. It is my experience that deaf or very hard-of-hearing persons lack tickling sensations in the meatus;[5] this observation, which has been confirmed by many authors (Kompanejetz[6]), cannot be used for more than a tentative diagnosis because it does not hold true in every case of deafness or hardness of hearing. According to Kompanejetz,[6] this symptom is especially significant of congenital deafness. It seems to be of rather a pathoanatomic interest since the method of direct tone introduction has been used. I mention it here because in some of my early cases of psychic deafness in children, 1 of which I shall describe here, the diagnosis was made on the basis of the presence of the tickling sensation only.

REPORT OF CASES

It seems worth mentioning that I have seen only 12 psychically deaf children, although my experience with patients with speech and voice disturbances covers over 60,000 cases. Is the condition in question really so rare, or is the differential diagnosis so difficult that many children may have been mistakenly considered as deaf? Regardless of whether or not one suspects that some so-called deaf persons belong to the group of the psychically deaf, one should exercise the greatest precaution in making the diagnosis of real deafness in children.

Of the 12 cases which I have encountered, I shall describe 3, 1 of these (case 1) only briefly because it has already been reported in detail.[7]

CASE 1.—A 4 year old boy who was suspected of being deaf showed but one symptom that with some probability spoke against organic deafness, namely, the tickling reflex. Three weeks of frequent attempts to obtain from him any response to acoustic stimuli passed without a positive result. Many musical instruments, such as trumpets, drums, the gramophone, whistles of the Urbantschitsch accordion and clocks, as well as the human voice, were employed—all without any recognizable response on the part of the patient. On the twenty-first day I rang a small bell 3 meters behind him. In a flash he turned around, and he frequently reacted similarly to the same bells during the following days. Then I used other bells, tuning forks and, later, horns and the human voice. Gradually the boy reacted regularly to all these stimuli by turning, looking at them and raising an arm, as he was asked to do. At the end approximately of another three weeks (eight to nine weeks after the beginning of the treatment) he could be awakened by tones and noises; this had never before been possible. After four months of treatment he began to produce smacking sounds. Babbling started and increased steadily. Four weeks later he began to imitate sounds and syllables, and after two more weeks he imitated all syllables and some monosyllabic words. After that his parents returned home with him, highly satisfied with the results of the treatment. They promised to report to me if the child's further development should not be satisfactory. No such report has come.

CASE 2.—A girl aged 6 years was brought to my clinic in Vienna because of deafness. She spoke a few words in a monotonous voice. The voice, while not exactly that of a deaf child, was nevertheless different from the normal voice. The family, as well as the personal, history did not furnish any explanation for the deafness. Neither deafness nor any mental or serious somatic disease had occurred among her ancestors. Birth had been normal, and so was her development except for deafness and poor speech. She was of normal weight and height. Neurologic tests and examination of the internal organs did not reveal anything pathologic. The drum membranes and the vestibular apparatus were normal. The direct tone introduction test was responded to with such strong tossing of the head that, after the first attempt, I immediately began to train the child to raise her arm in response to a tone heard at some distance from the ear. After fifteen minutes of training in this way I got a complete record of her hearing acuity. She heard every tone of the six octaves at at least 10 meters (the length of the room available) when the whistles were blown softly. After a few days she began to repeat sounds, syllables and words, but only at a distance of 2 to 3 meters. Nevertheless, according to the report of her parents, she did not react to any kind of acoustic stimuli at home. Therefore I decided to separate her from her usual environment for a time. There were boarding homes in Vienna which were conducted by people whom I had trained in the treatment of children with speech troubles.

The girl was admitted to one of these. Here, after only one week, she repeated every word spoken at a distance of 6 meters (the space available). After four weeks she not only repeated but spoke spontaneously many words, and even simple phrases, in a normal voice. When she was brought home again, she continued to speak and to react to all acoustic stimuli. Dr. Mohr, of my staff, trained her at regular intervals for several months, until she was accepted into a grammar school. For about a year I did not see her. Then the mother came to me in despair to tell me that the child had gradually stopped hearing and that she had

5. Froeschels, E.: Zur Differentialdiagnose zwischen Taubstummheit und Hörstummheit, Med. Klin. **6**:2051-2052, 1910.

6. Kompanejetz, S.: Ueber das Froeschels'sche Kitzelsymptom bei Taubstummen, Monatschr. f. Ohrenh. **59**:679-687, 1925.

7. Froeschels, E., and others: Psychological Elements in Speech, translated by N. Ferre, Boston, Expression Company, 1932, pp. 78-80.

been admitted to the department of health of the children's hospital of the university. There she was said to be absolutely deaf. I made contact with the head physician, the late Dr. Lazar, who brought the child to my department. To my surprise, as well as that of my staff, she reacted only to direct tone introduction. Her reactions consisted merely of blinking. No change either of the drum membranes or of the vestibular apparatus was noticeable. All our attempts to restore the hearing succeeded only moderately. After a treatment with systematic hearing exercises she repeated words at a distance of 1 to 2 meters. She had to be admitted to a school for the hard of hearing.

CASE 3.—S., a girl 2 years and 5 months of age, came to me on March 7, 1941. The psychiatrist, Dr. Adolf Zeckel, who accompanied her, wanted me to discover if possible the reason for her dumbness, as well as her peculiar behavior. Although the child, according to the reports of the parents and the physician, had never responded to acoustic stimuli, Dr. Zeckel once saw her looking up when an airplane passed high in the sky. The mother had noticed that the child turned occasionally when some one called her name. Once she turned to the side where a bell rang, a short distance from her. Certainly, her behavior was abnormal in every respect. She had no toilet manners and no sense of cleanliness, and she manifested a strong desire to break and destroy her toys, as well as plates and glasses. Any toy could fix her attention and interest only for a few minutes. She hardly ever handled one of them in the proper manner. The most alarming symptom to the parents and the physicians was the child's habit of striking herself on the head and in the eyes almost all day long. All these facts led to the suspicion of feeblemindedness. The family history did not offer me much encouragement for a good prognosis. Several of the mother's cousins on her father's side were congenitally deaf. The older brother of the child, 2 years her senior, and the parents were normal, however. In the history a few facts seem worth a detailed description, among them the child's reaction on being weaned. When she was 6 months old, the mother started to wean her by gradually substituting other food for the breast milk. The child refused all other food, spitting it out, and when her mother forcibly put food into her mouth, the child would turn over on her stomach and empty her mouth with her fingers. As there was no longer breast milk, the girl almost starved, and only gradually accepted some buttermilk with flour and sugar. At this time she stopped the babbling which had started about two months before. When the family was forced to flee from the Fatherland, she refused food completely and almost starved to death. Only slowly she began again to take strained food. Half a year after the flight she showed no gain in weight. Another important fact in the history is the mother's report that she noticed early that the child turned her head or looked up only infrequently when her name was called, and never when any kind of noise was made near her.

When I first saw the child, she was of normal height and weight but very pale. It was almost impossible to fix her attention, even for the shortest time, on colored pictures or toys or with whistles, bells or tuning forks. She was restless, punched her own eyes and cried. Once, however, I succeeded in putting the ear olive into the meatus of her left ear and in testing her hearing for one tone of the first small octave. She reacted to this by withdrawing her head so strongly that I got an impression which differed from that received from very hard-of-hearing children and was reminded of "psychic deafness." During the following days I tried to gain her friendship by showing her again and again different colored pictures and toys. In this way I succeeded in seating her on a chair for several minutes. Her interest in the pictures and toys evidently grew, and after a few days she did not object to coming into the treatment room without her mother.

March 14, 1941: g blown at a distance of 1 meter produced no reaction, but she turned immediately to look at the whistles a and c-2 blown 1 meter behind her.

March 16: She gave the same positive response to f, a, e-1 and g-2 blown at 1.5 meters, but no reaction to e and g.

March 19: A was heard at a distance of 1.5 meters.

During these days, and during the subsequent ones, pictures and toys, which I named, were shown to her. In March 31 she permitted me, for the first time, to put the ear olive into one or the other meatus and listened with evident interest to the tones of the different whistles, as well as to scales, tunes and single tones which I sang. The scales and other tones were introduced into the ear by means of the same rubber tube, the other end of which was adjusted to a funnel. Into this funnel I placed my lips. This kind of treatment, as well as that with the whistles, was continued every day for two months. The child began to like the "direct tone introduction," and I gradually could progress to increasingly softer blowing and singing and still get some response from her, namely, attentive listening and incidental smiling.

At the end of these two months she also listened attentively to knocking at the top of the desk and to small bells at a distance of 1.5 to 2 meters. At this time she produced a kind of speech consisting of some almost exactly articulated sounds. The voice sounded normal to me. This fact, in addition to the progress of her hearing, gave hope that no serious organic hardness of hearing was present.

April 23: The girl listened attentively to two alternately blown whistle sounds; one week later she imitated Sh-Sh-Sh (an engine's noise) with F F F. At this time I began to work with phonetic pictures each of them showing the face of a child articulating one speech sound. I accompanied each picture with a loud pronunciation of the corresponding sound. At the end of May she spoke after me Ah, O, E, W, B and M. Two weeks later she repeated the following words: wood (as woo); wheel; tree (as tee); piano (as p).

During the following two months the child's skill in repeating steadily grew. At this time I tried to make her choose on command one of two toys. She succeeded sometimes, but, in consideration of the many mistakes, it was questionable whether the positive results were not due purely to chance. She certainly showed signs of intelligence, e. g., in putting small weights of different sizes into the holes of a wooden box, each hole being just large enough for a certain weight. The striking of her head and eyes had stopped completely; she frequently smiled in a friendly way at people and generally was in a good mood. During the summer of 1941 she spoke after me 35 to 40 words more or less correctly almost every day. Only rarely did she need optical help, namely, watching the movements of my mouth, for this purpose. Usually she repeated in the acoustic way at a distance of 1.5 meters. Suddenly, at the beginning of September 1941, she stopped every attempt at repeating, and this behavior persisted throughout the following six weeks. Not only did she stop repeating, but she did not react to tones or noises or to my voice. Sometimes I had to take her by

surprise, and ring a bell behind her, to confirm the correctness of my diagnosis of "psychic deafness."

After this period she started again a self-invented speech, containing many correctly articulated common sounds and a melody resembling that of short phrases. Toward the end of 1941 her willingness to repeat words (the names of the colored pictures, which I always used) suddenly returned, and on Jan. 22, 1942 I noticed that she repeated the words man, wheel, car, door, pen (as en) and letter, one after the other.

On January 26, the Merrill-Palmer test was administered to her in the Psychological Testing Center (New York). Part of the report follows: "S. seemed to enjoy the form boards and revealed good perception of forms. She worked quickly and skilfully in fitting the various pieces into the proper spaces. Observation revealed that she was dominantly left handed. . . . It is questionable how much she could hear and . . . how much this factor affected the total result. She was somewhat emotionally disturbed, . . . and she did not therefore devote her best efforts to the task presented."

In the next five months her skill in repeating steadily grew. Besides, her shyness in speaking in the presence of strangers, which made her a poor subject for demonstrations, gradually disappeared, and on July 3, 1942, she repeated 40 words in the presence of a speech teacher. These words contained all the sounds common in English.

In the fall of 1942 there was another relapse, in the form of unwillingness to repeat and lack of interest in acoustic stimuli. With the unhappy experience in case 2 in mind, I always had to assure myself of her hearing acuity by using surprise situations, to which she reacted positively. After an intermission of about five weeks in which she did not speak she suddenly began to repeat words again. Her understanding of speech was still poor; only occasionally she chose the right toy from a choice of two if ordered to do so.

During the following months a remarkable change occurred with regard to her ability or willingness to repeat: She repeated one and two syllable words, then stopped doing it for days or weeks and did not give reliable proof that she knew the name of the toys. But her hearing acuity increased gradually to such an extent that she repeated words which I whispered to her.

Late in the spring of 1943, Dr. Potocky, whom I consulted for an examination of the nail capillaries, found some primitive forms among them and ordered administration of a 2 grain (0.13 Gm.) tablet of anterior pituitary daily. She spent two months of this summer at a camp. According to her mother's report, she began to make a few friendly contacts with the other children in her second week there. "She repeated willingly enough what she was told to say, but did not show any initiative in saying or repeating things when she did not get special orders to do so."

If one considers her initial deafness, which certainly was of central origin, many of the clinical features can easily be understood. To be sure the normal function of Wernicke's center depends on the absence of any kind of severe trouble in the middle ear, the labyrinth, the acoustic nerve and its center,[8] and, of course, on a normal condition of Wernicke's center itself. In S.'s case one must assume the presence of a gradually decreasing defect in the acoustic center. Not before this trouble had been reduced to one of moderate degree could any regular "charging" of Wernicke's center be expected. Experience with normal children shows that this "charging" must reach a certain strength before understanding of speech, spontaneous repeating of words and spontaneous speech occur. No wonder, therefore, that S. repeated only to order and that her understanding of words was poor, as shown by her frequent mistakes in choosing the right toy from two offered her.

Now, in the fall of 1943, a remarkable turn for the better has been noticed with respect to word understanding, as well as spontaneous repetition. She now almost never fails in choosing, on order, the right toy out of twenty or more. She frequently repeats words spontaneously. I do not doubt that the continuation of this systematic treatment finally will result in normal speech understanding and in spontaneous speaking, all the more as her intelligence, as well as her general behavior, have been changing and now are almost normal.

8. It suffices if one ear and the corresponding hearing center are in good condition.

COMMENT

The 3 patients whose cases have been reported, although differing in their responses to the treatment seemed to have in common an initial deafness, and they gained ability to hear by psychologic treatment and by hearing exercises. The same results could be reached by the same method in the other patients whom I have seen.

As there exists nowhere in the literature an anatomic description of the underlying condition in the central nervous system, any explanation of the cause or causes of the clinical picture will necessarily be hypothetic. In view of the rapid change of the clinical picture in case 2 at the beginning of the treatment, one naturally thinks of the pure resistance to that part of life which enters consciousness acoustically. A kind of psychic shock might be assumed to be responsible for this behavior; in other words, one might try to identify the "psychic deafness" in children with hysterical deafness. But case 2 was chosen because the suddenly invoked normal hearing turned into permanent hardness of hearing. There was no disease of the middle ear, and the vestibular apparatus was not affected. Whether there occurred a disease of the inner ear, in other words, a disease of the acoustic nerve, or simply a destructive process in Heschl's center or in the central acoustic pathways[9] cannot be decided by modern otologic methods. The child had no acute infectious disease at the critical time. All these data may support the assumption that a degenerative process in the acoustic centers was the cause of the decreased acuity of hearing. From this assumption, it is easy to conclude that the initial deafness was due to a slight anatomic disturbance of these centers, which kept them in a state of inactivity. One, nevertheless, is right in assuming

9. For anatomic orientation see Morel, F.: L'audition dans l'aphasie sensorielle, Encéphale **30**:533-553 (Oct.) 1935; The Neural Mechanism of Hearing: Symposium, Laryngoscope **47**:365-491 (July) 1937.

that a psychic component in the initial deafness also existed.

In case 3 hearing improved slowly, the progress reminding one of the gradual improvement obtained by systematically applied auditory exercises in some organically hard-of-hearing people. Experts agree that in persons of the latter type improvement in hearing is due chiefly to awakening the attentiveness to acoustic stimuli, in other words, to educating the centers to function up to their highest capacity. The parallelism between these cases and that of S. might justify the supposition that the educational work on the hearing centers of S. was responsible, at least in part, for her progress. On the other hand, her case suggested the presence of another powerful factor in her deaflike behavior, namely, a psychic resistance to acoustic stimuli. Her frequent relapses into acoustic inactivity have made that impression, all the more because they have suddenly passed over into the hearing acuity present prior to the relapse.

In case 1 the gradual improvement of the hearing seems to indicate the presence of a pathologic central condition.

Even if these hypothetic explanations are acceptable, I must still concede that some problems involved in my thesis cannot be answered even hypothetically. Why, for instance, did the first patient react to a certain instrument, after many fruitless attempts on my part to awaken his attention with numerous other stimuli? The pitch of the tone could not be responsible for his positive reaction, as the same pitch had been used frequently before. And, suppose that the assumption of a pure psychic component is correct, why did the second patient during the first series of treatments never relapse into deafness, and why did the third patient so frequently do so?

Before I try to make clear the idea that a slight defect in Heschl's convolution may produce an aversion to hearing, I wish to show how inactivity of the normal Heschl center can create the picture of deafness. I observed a 10 year old girl, the daughter of two congenitally deaf parents, whose reaction was like that of a deaf person in spite of a normal hearing organ. The girl, the youngest of 3 children, was considered deaf by persons in her environment because the parents and the two older children could not hear. She therefore learned to communicate with her family and with other people by means of the sign language. To the great surprise of her parents, and, I suppose, to her own, her hearing acuity proved to be normal at the first examination with the Urbantschitsch whistles. It was nothing but the inactivity of her hearing centers that made her appear deaf. Stein[10] reported a similar case.

I shall now try to explain hypothetically the psychic component of "psychic deafness in children" as a consequence of a slight defect in Heschl's convolution. Normally developed centers in infants somehow receive the adequate stimuli from the outer world, as a sponge absorbs water. No active collaboration of the will can be assumed at the earliest period of life. The centers become charged purely in a passive way. Surely, some associations between impressions received by the centers originate also passively. When the first mental activities are demanded by the environment, such as those involved in the child's sitting up, taking the first steps, showing "how big he is" or repeating words, such demands find the mind somehow prepared by the impressions passively acquired. One might even speak of an overabundance of former impressions which demand of themselves an active "discharge." But if a center is not normally adjusted, everything, or at least much, that is asked of the child will be more than he can do. This disproportion between inner readiness and demands from the "outside" must, naturally, lead to a feeling of uneasiness on the part of the child. This feeling might appear as resistance, opposition and still greater isolation than that caused by the missing function of the center in question.

So the psychic component in the clinical picture seems to be the natural consequence of the primary defect. Their influence on one another will increase the inactivity of the centers, as well as the aversion to hearing.

That occasionally a psychic shock may contribute to the abnormal behavior cannot be denied, all the more as a *punctum minoris resistentiae* is the more easily susceptible to shock.

Finally, the term "psychic deafness in children" does not seem well chosen because an organic, though slight, defect of Heschl's convolution appears to be primarily responsible for the trouble. In looking for a better name, one may think of "auditory agnosia," which, as defined by Nielsen,[11] is loss of power to recognize heard sounds. But Nielsen himself identified the disorder with Wernicke's "aphasia," which consists of a loss of perception of *words*, due to a subcortical lesion in the neighborhood of the center for word pictures. Although this aphasia frequently is combined with defective appreci-

10. Stein, L.: Speech and Voice, London, Methuen & Co., Ltd., 1942, p. 98.

11. Nielsen, J. M.: Epitome of Agnosia, Apraxia and Aphasia with Proposed Physiologic-Anatomic Nomenclature, J. Speech Disorders **7**:105-141 (June) 1942.

ation of noises and other auditory stimuli,[12] it is by no means identical with central tone deafness. For the latter, consequently, the term "auditory agnosia" cannot be used. I suggest that the name "psychic deafness in children" be replaced by that of "central deafness," as it signifies better the underlying condition.

SUMMARY

The term "psychic deafness in children" has been applied by other authors to youngsters who seemed to be deaf but could be cured without otologic or other treatment for an organic disorder.

The method of testing the hearing acuity of even very young children and of hard-of-hearing children described here, in contrast to the audiometric method, does not require the active collaboration of the child being examined.

The tickling reflex has significance for the probable diagnosis of deafness in children.

It is probable that the basic trouble in psychic deafness in children consists of a slight defect of Heschl's convolution. This defect can most easily create an aversion to auditory impressions. Both these components may form a vicious circle, so that gradually the clinical picture is aggravated.

With respect to the basic trouble, the term "central deafness" seems more adequate than "psychic deafness."

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12. For a survey of the literature see Weisenburg, T., and McBride, K. E.: Aphasia: A Clinical and Psychological Study, New York, Commonwealth Fund, 1935, p. 64.

PROLONGED INSULIN COMA IN TREATMENT OF SCHIZOPHRENIA

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The syndrome of prolonged coma is a phenomenon occasionally encountered during the course of insulin therapy as used in selected cases of schizophrenia. It is a complication which becomes obvious when the induced hypoglycemia is terminated by the administration of dextrose in quantities sufficient to bring about hyperglycemia. The picture differs from that of the usual uncomplicated recovery which follows the hypoglycemic state in that its criteria are: (1) normal blood sugar or induced hyperglycemia; (2) a shifting neurologic picture; (3) peripheral manifestation of fluctuant control of the autonomic nervous system, such as alterations in regulation of heat, disturbances in cardioregulatory function, sudomotor hyperactivity and hyperpnea, with consequent tetany; (4) convulsive phenomena or their equivalents; (5) prolonged coma, and (6) associated with recovery of consciousness, disturbances in the sensorium, alterations in memory function and a quantitative reduction in all higher cortical functions. The last-mentioned psychopathologic residua reflect the widespread cytologic changes which are demonstrable histologically in the brain tissue. We have correlated certain observations in an attempt to explain the occurrence of prolonged coma on a physicochemical basis.

We suggest a mechanism for insulin shock which is based on the assumption that the demonstrable histopathologic and physiologic changes which accompany hypoglycemia induced by large doses of insulin may be explained on a basis of physical, biochemical and colloidal changes. We believe that, as a result of certain physicochemical processes, there is progressive cellular hydration. We conceive this process to be a reversible one, dependent on certain variables and accomplished by the restoration of the normal dextrose substrate. However, if this point of simple reversibility is passed, additional agents must be employed to restore the cellular balance, and in cases in which the progressive hydration has been excessive all efforts at restoration of normal cellular function fail and death of the cell follows. The location, the size and the phase of the lesion, we believe, determine the variable and shifting neurologic picture, as well as the morbidity and the mortality rate.

From the Markle Unit of the Pennsylvania Hospital.

CLINICAL CONSIDERATIONS

In this presentation of 51 periods of prolonged coma occurring in 38 patients, it must be emphasized that all patients received a solution of dextrose intravenously in sufficient amounts to raise the blood sugar to a normal level or above; with the majority of the patients this was confirmed by determination of the level of the blood sugar. If the patient failed to respond, provided his blood sugar was normal or above, and a sufficient period of time (fifteen to twenty minutes) had been allowed for the cellular utilization of the dextrose, the condition was judged to be prolonged coma. Excellent clinical descriptions of this complication have been given by Binzley and Anderson,[1] Freed and Saxe,[2] Rossman and Kline [3] and Easton.[4]

Goldman,[5] in a series of 108 patients, reported an incidence of 23 prolonged comas; in 17 per cent of the patients treated this complication developed. Kant,[6] in a series of 61 patients, encountered prolonged coma in 9, i. e., in 15 per cent. In our series of 225 insulin-treated patients, the 38 who manifested prolonged coma represented an incidence of 17 per cent.

In Lester's [7] series of 24 cases of prolonged coma the mortality rate was 16 per cent. The

1. Binzley, R., and Anderson, J. L.: Prolonged Coma in Insulin Treatment of Dementia Praecox, Psychiatric Quart. **12**:477, 1938.

2. Freed, H., and Saxe, E.: Prolonged Non-Hypoglycemic Coma Occurring During the Course of Insulin Shock Therapy, J. Nerv. & Ment. Dis. **90**:216, 1939.

3. Rossman, I. M., and Kline, W. B.: The Pharmacological "Shock" Treatment of Chronic Schizophrenia, Am. J. Psychiat. **94**:1323, 1938.

4. Easton, N.: A Case of Protracted Hypoglycemia, Am. J. Psychiat. **91**:853, 1938.

5. Goldman, D.: Prolonged Coma After Insulin Hypoglycemia: Clinical Features and Treatment, J. Nerv. & Ment. Dis. **92**:157, 1940.

6. Kant, F.: Protracted Shocks Occurring During Insulin Shock Therapy and Their Treatment, J. Nerv. & Ment. Dis. **91**:712, 1940.

7. Lester, D.: A Study of Prolonged Coma Following Insulin Shock, Am. J. Psychiat. **95**:1083, 1939.

51 prolonged comas in our series resulted in 2 deaths, or a mortality rate of 5 per cent.

The impression that prolonged coma, though dangerous, had a beneficial effect on the mental status of the patient is not borne out by the rate of recovery in this series of 38 patients. Fifty-one per cent of these patients had "total or social remission." This figure is slightly less than the recovery rate for our total series of patients. It must be mentioned, however, that there was some improvement in the mental status of about two thirds of the patients immediately after their prolonged coma.

The age and sex of the patients with prolonged coma was without statistical significance; the distribution was similar to that of the entire series of insulin-treated patients.

The length of time patients are allowed to remain in hypoglycemic stupor before dextrose is administered has been stressed in a number of reports; it has been recommended that insulin stupor be terminated at the end of one to one and a half hours.[8] Since our patients are routinely allowed to remain in stupor for two hours, it is difficult to explain why only 17 per cent, and not many more, had prolonged coma. Patient 10 (table) was not in stupor prior to the time he was given dextrose orally, with the intention of terminating his treatment for that day. He immediately passed into a deep coma, which was unaffected by the intravenous administration of an adequate amount of dextrose. In other patients a prolonged coma developed despite the fact that their therapeutic stupor was of less than one hour's duration.

The quantity of insulin, both the individual and the cumulative dose, has been mentioned as an etiologic factor in the production of prolonged coma. The range in individual doses of from 55 to 400 units and the range in the cumulative dose of from 275 to 10,685 units, as reported in the table, while not conclusive proof, makes such an assumption doubtful. Also, it is noteworthy that when these patients were again treated, after their successful recovery from a prolonged coma, the dose of insulin was often increased beyond the level at which the patient originally went into prolonged coma, without a secondary recurrence. With these patients, neither the individual nor the cumulative dose could be regarded as the main factor determining prolonged coma.

Estimation of the depth of a hypoglycemic stupor is a matter of clinical judgment. Certainly, no attempt was made to produce a deeper stupor in these patients than in patients of the control series. With respect to the neurologic criteria, the corneal reflex was elicited in 37 of the 38 patients when dextrose was administered at the termination of the daily treatment. With 37 of the 51 prolonged comas the dose of insulin on the day prolonged coma was induced was the same as, or lower than, it had been on the preceding day. It appears that, if there was an increase in the depth of stupor on the day of prolonged coma, it was due to an unusually pro-

Data Concerning Fifty-One Periods of Prolonged Coma Occurring in Thirty-Eight Patients

Patient No.	Day of Stupor	Hours of Treatment on Day of Stupor	Dose of Insulin on Day of Prolonged Coma, Units	Total Dose of Insulin, Units	Period of Prolonged Coma, Hr.	Results of Treatment *	Therapy for Hypoglycemia †
1	5	2	115	895	2	S R	S
2	3	2	90	345	14	....	S
	3	2	55	275	4	I	S P
3	26	2	175	4,555	5	U	S P
4	28	2	190	5,490	3	....	S
	56	2	210	10,685	5	U	S
5	2	2	130	805	9	S R	S
6	5	2	145	800	8	....	S P
	6	2	140	980	13	....	S P
	23	2¼	115	3,280	5	S R	S P
7	4	¼	180	1,300	7	U	S
8	1	2	380	2,860	13	....	S P
	21	2	330	8,970	3½	....	S P
	26	2	310	10,520	5	I	S P
9	36	¾	270	10,620	10	S R	SO
10	0	0	125	625	8	T R	SO
11	3	2	190	1,070	21	S R	S P
12	49	2	185	8,250	6	T R	S
13	23	2½	180	3,655	78	I	S SO
14	2	1½	170	730	20	....	S P
	10	2	120	1,530	3	....	S P
	12	1	90	1,710	2	....	S P
	15	2	80	1,950	3	I	S P
15	21	2	120	3,100	34	D	
16	7	2	100	950	14	T R	S
17	7	2	200	2,360	4½	....	S
	8	2	190	2,550	3	S R	S
18	15	2	260	4,380	2	S R	S P
19	29	2¼	200	6,950	5	S	S SO
20	16	2	230	4,345	2	I	S
21	40	2	140	6,170	7	U	P
22	2	2	150	550	4½	....	P
	4	2	140	830	5	D	
23	14	2	160	2,480	5	S R	S P
24	40	2	185	6,390	3	U	P
25	24	2	190	5,180	24	S R	S
26	4	3	165	1,135	2	T R	P
27	3	2¼	155	930	14	I	S
28	7	2	340	3,040	7	....	S P
	20	2	330	7,270	3	S R	S P
29	28	2¼	130	3,260	1	S R	S
30	8	2	185	2,045	8	I	S
31	16	2	245	4,210	8	I	S
32	36	2	240	9,010	1½	U	P
33	8	2	140	1,460	8	S R	S P
34	11	2	200	2,750	5	....	P
	31	2	180	5,850	48	U	P
35	5	2	130	620	5	S	S SO
36	25	1	135	3,340	12	U	S P
37	9	2	170	1,800	2	S R	P
38	18	2	400	8,770	7	U	P

* T R indicates total remission; S R, social remission; I, improvement, and U, no improvement.

† S indicates sucrose; SO, sorbitol; P, plasma; S P, sucrose and plasma, and S SO sucrose and sorbitol.

8. Wortis, J., and Lambert, R.: Irreversible or Hyperglycemic Insulin Coma, Am. J. Psychiat. **96**:335, 1939.

found reaction of the patient to the same, or to a smaller, dose of insulin.

A number of pertinent factors must be considered in an attempt to establish the role of certain variables in the production of the syndrome:

1. For the patients in whom prolonged coma developed the average duration of therapeutic stupor was equal to that for the control patients.

2. There was no correlation between the total or the daily amounts of insulin given the control patients and the amounts given the patients with prolonged coma.

3. In 33 of 38 patients with prolonged coma a deep stupor was not produced.

4. In a large percentage of the patients deeper stupors had previously been produced without complications with smaller doses of insulin.

Therefore, it becomes apparent that the decisive factor is none of these factors but, rather, the total reaction of the patient at a given time. Theoretic considerations make it reasonable to assume that the state of water balance and its related factors account for the development of prolonged stupor.

Easton [4] stated that a certain type of patient, whom he described as "tall and asthenic, with cold, blue hands and feet," tolerated insulin poorly. We have become increasingly wary of patients in whom the subcutaneous fat is not firm, the peripheral veins are small and embedded and the skin is thin and waxy. The clinical impression was gained that certain patients were predisposed to water imbalance. The fact that 24 of the 51 prolonged comas occurred during the first ten days of stupor suggests that there is a tendency on the part of certain patients to manifest this complication when other provocative conditions, such as a large dose of insulin and long or deep therapeutic stupor, are rapidly established. Certain patients have shown no tendency to prolonged coma with a high dose of insulin with long or deep therapeutic stupor; these patients we have considered as having a more stable water metabolism.

THERAPEUTIC CONSIDERATIONS

Treatment of the syndrome of prolonged coma is based on an attempt to correct the pathophysiologic basis. Dextrose must be supplied to stop the progression of cellular depletion of the sugar. This may be accomplished most quickly by the intravenous administration of a solution of dextrose and supplementary gavage. We agree with Kant [6] that once the blood sugar has been raised to normal there is no advantage in the continued administration of dextrose. In cases in which the coma is extended care must be taken to maintain a normal degree of glycemia.

The use of dehydrating agents in the treatment of the complication of hypoglycemic stupor in experimental animals was first suggested by Drabkin and Shilkret [9] and Drabkin and Ravdin.[10] One of us (T. D. R.)[11] reported on the use of 50 per cent sorbitol and 50 per cent sucrose in the management of the convulsions complicating insulin hypoglycemia in patients under treatment.

In the present series, dehydrating substances were given as prophylactic agents to patients who had had a previous prolonged coma or in whom such a complication was feared. Under these circumstances, the substance was given one half to three quarters of an hour before the regular administration of dextrose. The patients who failed to respond within fifteen minutes after an intravenous infusion of dextrose received an additional injection of 50 to 100 cc. of 50 per cent sucrose.[12] Usually there was a distinct change in the severity of the coma during the next half-hour. Masserman,[13] in his original work on the dehydrating action of polysaccharides, observed that the effect decreased after three hours. We have noted the same phenomenon. Patient 30 (table) was given sucrose and was aroused about two hours later, only to lapse back into coma, from which she was again aroused by a second administration of sucrose. This was repeated three times during the twelve hours she was in coma, before final recovery. It is now our practice to repeat administration of the sucrose every three hours during the first twenty-four hours the patient is in coma.

Concentrated lyophile serum has been used to reduce cerebrospinal fluid pressure;[14] it also relieves cerebrocellular edema. Its action is

9. Drabkin, D. L., and Shilkret, H.: Anhydremia with Insulin and Water Intake, Proc. Soc. Exper. Biol. & Med. **22**:369, 1925.

10. Drabkin, D. L., and Ravdin, I. S.: The Mechanisms of Convulsions in Insulin Hypoglycemia, Am. J. Physiol. **118**:174, 1937.

11. Rivers, T. D.: Effect of Vitamin B_1, Sucrose and Sorbitol on Certain Complications of Insulin Hypoglycemia: A Clinical Report, Arch. Neurol. & Psychiat. **44**:910 (Oct.) 1940.

12. Sucrose for this study was supplied by Eli Lilly and Company, Indianapolis.

13. Masserman, J.: Effects of Intravenous Administration of Hypertonic Solutions of Sucrose, with Special Reference to Cerebrospinal Fluid Pressure, Bull. Johns Hopkins Hosp. **57**:12, 1935.

14. Hughes, J.; Mudd, S., and Strecker, E. A.: Reduction of Increased Intracranial Pressure by Concentrated Solutions of Human Lyophile Serum, Arch. Neurol. & Psychiat. **39**:1277 (June) 1938. Wright, D. G.; Bond, D. D., and Hughes, J.: Reduction of Cerebrospinal Fluid Pressure by Concentrated Lyophile Serum: Further Observations, ibid. **39**:1288 (June) 1938.

much more prolonged (six to eight hours) and powerful, and it has the additional virtue of being a derivative of a physiologic agent. An efficient dehydrant would be expected to arrest the sequence of events when cerebrocellular edema is a pathologic factor. The usual technic of administration has been to dilute the lyophile plasma [15] (the equivalent of 125 cc. of whole blood) with 50 cc. of distilled water and to administer this intravenously in a 50 cc. syringe. More recently, however, we have used 50 cc. of 50 per cent solution of sucrose as the diluent, with potentiation of its dehydrating effect. To date, none but beneficial reactions from this treatment have been observed. There were 2 deaths in 51 comas treated with this method. The statement has to be qualified, since in both patients the regimen of dehydration had been discontinued; 1 patient received a transfusion of whole blood, and 1,000 cc. of isotonic solution of sodium chloride was given the other patient by intravenous infusion a few hours prior to death.

In a statistical review of the therapy employed in the 49 cases of prolonged coma, the 2 instances of the death being omitted, we obtain the following data: Sucrose alone was used in the treatment of 17 comas; sorbitol alone, in the treatment of 2 comas, and plasma alone, in the treatment of 9 comas. Plasma and sucrose were used in the treatment of 18 comas, and sorbitol and sucrose, in the treatment of 3 comas.

In none of our cases were the results of treatment of the coma dramatic, but in all instances clinical improvement was observed within the hour following the medication. The absence of dramatic results would be expected in view of our theory of the cause of the stupor. A comparison of Lester's [7] report of 24 cases, with a mortality rate of 16 per cent, leads to the conclusion that our own mortality rate of only 5 per cent was due to the difference in treatment.

We have used oxygen and carbon dioxide in overcoming the alkalosis incident to hyperpnea, which, if untreated, seriously handicaps attempts to restore the acid-base balance. However, we did not find it necessary to use oxygen and carbon dioxide routinely in our treatment of prolonged coma.

It is necessary that the hemoconcentration and loss of chlorides due to profuse sweating and the outpouring of large quantities of chlorides into the lumen of the gastrointestinal tract, be counterbalanced by the appropriate administration of the salts. However, it must be borne in mind that hemoconcentration can exist in the presence of pronounced tissue edema, as is seen with surgical shock.[16] The immediate assumption that total deprivation of water exists is not justified on the basis of the observation of hemoconcentration in isolated samples of systemic blood. Indeed, administration of isotonic or hypotonic fluid might be expected to lead to a preferential local (cerebral) increase in intracellular edema, since the brain, by virtue of its low resistance to hypoglycemic injury, has been made the more vulnerable. One of our cases clearly illustrates this. The patient, after active dehydration roused for three hours; inadvertently, he was given 1,200 cc. of orange juice; after this a second coma intervened, which was again interrupted by repetition of the procedure of dehydration.

Adrenal cortex extract has been suggested [8] in the treatment of unremitting coma, and its rationale may well rest on its well known restitutive effect on water imbalance. Lewis and associates [17] demonstrated the hypersusceptibility of adrenalectomized animals to insulin-induced hypoglycemia. The potassium diuresis seen after the administration of adrenal cortex suggests it as an additional agent in the treatment of this type of shock. Freed, Shlesser and Lindner [18] called attention to the qualitative differences obtained with the various preparations of the adrenal gland in the treatment of shock. According to these authors, desoxycorticosterone combats successfully shock due to shifts in body fluids.

An attempt will be made to reconstruct the pathophysiologic basis from the existing reports and the knowledge available as to the mode of action of insulin in large doses.

PATHOLOGIC CONSIDERATIONS

The question whether insulin itself produces demonstrable lesions in tissues has been answered in both the negative and the affirmative. Tyler stated that insulin itself is histiotoxic and that the associated metabolic changes contribute still further to the neuropathologic and pathophysiologic changes. Schereschewsky, Mogilnitzky and Gorjaewa [19] expressed the opinion that in-

15. Sharp and Dohme, Inc., Philadelphia, supplied lyophilized blood plasma for this study.

16. Blalock, A.: Principles of Surgical Care: Shock and Other Problems, New York, Oxford University Press, 1940. Moon, V.: Shock and Related Capillary Phenomena, St. Louis, C. V. Mosby Company, 1940. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

17. Lewis, R. A.; Thorn, G. W.; Koepf, G. F., and Dorrance, S. S.: The Role of Adrenal Cortex in Acute Anoxia, J. Clin. Investigation **21**:33, 1942.

18. Freed, S. C.; Shlesser, I., and Lindner, E.: Relationship of Steroids of Adrenal Cortex to Shock, J. A. M. A. **118**:1403 (April 18) 1942.

19. Schereschewsky, N. A.; Mogilnitzky, B. N., and Gorjaewa, W. A.: Zur Pathologie und pathologischen Anatomie der Insulinvergiftung, Endokrinologie **5**:204, 1929.

sulin in large doses is a sympathotropic poison and a blood vessel toxin. But Schmid [20] attributed the sympathotonic manifestations to a hyperadrenalinemia provoked by and compensating for the administrated insulin. Weil, Liebert and Heilbrunn [21] stated the belief that they had found a definite relation between the occurrence and severity of the histopathologic changes and the cumulative amount of insulin their experimental animals received in the course of treatment. Yannet [22] brought evidence to bear that insulin itself, and not anoxia, with its corollary changes in the autonomic nervous system, is responsible for the pathologic damage. But both Salm [23] and Fortuyn [24] expressed the opinion that hypoglycemia, rather than insulin itself, produces diencephalic lesions, with consequent sympathetic and parasympathetic manifestations as terminal sequelae. Himwich and associates,[25] Wortis,[26] Gellhorn [27] and others have shown that with the deprivation of the dextrose substrate cellular respiration is reduced to a point of virtual anoxia. This, they claimed, is the method by which insulin produces its effect. Katzenelbogen,[28] in his review of the effects of insulin hypoglycemia, stated merely that irreversible structural alterations in the central nervous system of animals and men are provoked by such shock therapy. From the welter of data on insulin-provoked hypoglycemia it may be inferred that the cells have been disturbed functionally to such a degree that the syndrome produced is of an organic reaction type. To the clinical and pathologic picture must be added the disturbed electrolytic patterns and alterations in the electroencephalographic tracing noted by various authors.[29]

The conflicting histopathologic pictures described in the literature can be reconciled only by some such explanation as is here presented. If the histologic picture is considered merely as an arbitrary cross section of a dynamic process, one can account for the variously reported large, swollen cells, the pyknotic cells and the areas of devastation. Yannet [22] pointed out the difference between the changes which were seen in the brain cells of animals which survived a hypoglycemic episode and on which autopsy was done later and those in the animals on which autopsy was done immediately after the hypoglycemia. In the former, ganglion cells in the cortex, the basal ganglia and the upper part of the medulla were small, shrunken, pyknotic and dark staining, while in the latter, cells in this location were large, swollen and pale staining. In his excellent work on dogs, Yannet [22] claimed that he had demonstrated that during hypoglycemia there is a shift of water into the cells and that in animals which survived the cerebrocellular damage for several days there was a return of this water to the extracellular spaces, so that a shrunken cell, with enlargement of the intracellular compartment, was left. Grayzel [30] described, as occurring in rabbits subjected to hypoglycemia, "lesions consisting of zones containing shrunken hyperchromatic cells with corkscrew processes. The more severe lesions showed, in addition, zones of necrobiosis." All these rabbits had been treated for at least eighty-four days. Weil, Liebert and Heilbrunn [21] specifically called attention to the differences in the histopathologic picture seen when animals die in acute hypoglycemia and when they survive for a period of eighty days. This difference is similar to that seen by Yannet. These authors also called attention to large areas of devastation throughout the cortex and the cornu ammonis and, less frequently, the basal structures. MacKeith and Meyer,[31] in a case of death follow-

20. Schmid, H.: L'histopathologie du choc insulinique, Ann. méd.-psychol. **94**:658, 1936.

21. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

22. Yannet, H.: Effect of Prolonged Insulin Hypoglycemia on Distribution of Water and Electrolytes in Brain and Muscle, Arch. Neurol. & Psychiat. **42**: 237 (Aug.) 1939.

23. Salm, H.: Benommenheitszustände im Anschluss an die Insulinschockbehandlung von Schizophrenen, München. med. Wchnschr. **84**:1046, 1937.

24. Fortuyn, J. D.: Hypoglycemia and the Autonomic Nervous System, J. Nerv. & Ment. Dis. **93**:1, 1941.

25. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**:271, 1937.

26. Wortis, S. B.: Respiratory Metabolism of Excised Brain Tissue: The Effects of Some Drugs on Brain Oxidations, Arch. Neurol. & Psychiat. **33**:1022 (May) 1935.

27. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

28. Katzenelbogen, S.: A Critical Appraisal of the "Shock Therapies" in the Major Psychoses: II. Insulin, Psychiatry **3**:211, 1940.

29. Hoagland, H.: Electroencephalograms in Schizophrenia, J. Nerv. & Ment. Dis. **87**:337, 1938. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559, 1937. Cohn, R., and Katzenelbogen, S.: Electro-Encephalographic Studies, U. S. Nav. M. Bull. **37**:596, 1939.

30. Grayzel, D. M.: Changes in the Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694 (Nov.) 1934.

31. MacKeith, S. A., and Meyer, A.: Death During Insulin Treatment of Schizophrenia, with Pathological Report, J. Ment. Sc. **85**:96, 1939.

ing insulin treatment, observed foci in the deeper layers of the cortex in which the ganglion cells either had disappeared or were recognizable only as shadows. In other areas, the cells were shrunken, and the nucleolus was broken up into chromatin granules. To complete the pathologic picture, hypertrophy and hyperplasia of the astrocytes must be mentioned, and, with an increase in the intensity of cellular malnutrition, the glial reaction becomes most prominent.[32] Changes, probably secondary, in the vascular pattern have been reported. Cammermeyer [33] stated the belief that perhaps hypertrophy of the microglial nuclei is the only micropathologic change. De Morsier and Mozer [34] pointed out that the histopathologic alterations were not specific for insulin toxicity, but were similar to changes in the brain observed in other conditions and attributable to cellular anoxia.

The infrequency of occurrence, the location of the change and the very nature of the phenomena make precise evaluation difficult. But, if these histopathologic alterations are correlated with the electrochemical and physiologic changes taking place, an adequate explanation may be assumed.

Numerous investigators have studied the changes in electrolytes of the blood serum during hypoglycemic stupor. There have been variations in the magnitude of these changes, but all investigators agree that they are present and numerous. Katzenelbogen and associates [35] noted definite changes in the urea nitrogen, amino acid nitrogen, sugar, potassium, serum solids and inorganic phosphorus of the blood, as well as in the white cell count, the differential cell count and the viscosity, during insulin hypoglycemia. Spiegel and Spiegel-Adolf,[36] as well as others, showed that stimuli—mechanical, chemical, thermal or electrical—induce excitation in vivo by changing the ion concentration on the cell surface and subsequently in the cells. The tetany associated with the alkalosis of hyperventilation, the chloride deficiency of persistent vomiting and the disturbed calcium-phosphorus ratio in cases of parathyroid disease are examples of the heightened excitability of the nerve tissue in pronounced disturbances of the acid-base balance. We feel that the marked changes in the electrolytes of the blood serum accompanying insulin hypoglycemia act similarly to bring about the hyperexcitability and tetanic convulsions so frequently seen during stupor. The basis of electrolytic imbalance and increased cell permeability is probably the failure, due to lack of the dextrose substrate, of the metabolic processes necessary for maintenance of the dynamic equilibrium of the normal cell. Himwich and associates [25] and others [37] showed that in the presence of hypoglycemia there is a decrease in the respiratory metabolism of the brain which amounts to virtual cellular anoxia. This cellular anoxia, as Spiegel and Spiegel-Adolf [36] demonstrated, produces an increased permeability of the cell membrane. Cattell and Civin,[38] Baetjer,[39] Thaler [40] and Dennis and Moore [41] amply demonstrated that with local anoxia there is an increase in the level of serum potassium in the venous blood from such an area. Yannet [22] noted that in dogs subjected to hypoglycemia for a considerable period there are loss of cellular potassium and its replacement with sodium, which carries with it a large amount of water. In the studies of Katzenelbogen and associates,[35] no increase in the potassium of the serum was observed in the systemic circulation. However, there are mechanisms in the body which might prevent any systemic reflection of such release of potassium. Stewart and Rourke [42] noted an

32. Baker, A. B.: Cerebral Lesions in Hypoglycemia: Some Possibilities of Irrevocable Damage from Insulin Shock, Arch. Path. **26**:765 (Oct.) 1938. Finley, K. H., and Brenner, C.: Histologic Evidence of Damage to the Brain in Monkeys Treated with Metrazol and Insulin, Arch. Neurol. & Psychiat. **45**:403 (March) 1941. Weil, Liebert and Heilbrunn.[21]

33. Cammermeyer, J.: Recherches anatomo-pathologiques sur les lésions cérébrales dans la thérapeutique convulsivante de la démence précoce; par la méthode de Sakel (insuline); par le méthode de von Meduna (cardiazol), J. belge de neurol. et de psychiat. **40**:169, 1940.

34. de Morsier, G., and Mozer, J. J.: Lésions cérébrales mortelles par hypoglycémie au cours d'un traitement insulinique chez un morphinomane, Ann. de méd. **39**:474, 1936.

35. Katzenelbogen, S.; Harms, H. E.; Willmans, R.; Barkoff, S.; Brody, M. W., and Hayman, M.: The Insulin Treatment in Schizophrenic Patients: Clinical and Biochemical Studies, Am. J. Psychiat. **95**:793, 1939.

36. Spiegel, E. A., and Spiegel-Adolf, M.: Physicochemical Mechanisms in Convulsive Reactivity, J. Nerv. & Ment. Dis. **90**:188, 1939.

37. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: Mechanism of Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935. Spiegel and Spiegel-Adolf.[36] Wortis.[26]

38. Cattell, M., and Civin, H.: The Influence of Asphyxia and Other Factors on the Serum Potassium of Cats, J. Biochem. **126**:633, 1938.

39. Baetjer, A. M.: Diffusion of Potassium from Resting Skeletal Muscles Following a Reduction in Blood Supply, Am. J. Physiol. **112**:139, 1935.

40. Thaler, J. I.: Evidence of Permeability of Tissue Cells to Potassium, Proc. Soc. Exper. Biol. & Med. **33**:368, 1935.

41. Dennis, J., and Moore, R. M.: Potassium Changes in the Functioning Heart Under Conditions of Ischemia and of Congestion, Am. J. Physiol. **123**:443, 1938.

42. Stewart, J. D., and Rourke, G. M.: Intracellular Fluid Loss in Hemorrhage, J. Clin. Investigation **15**:697, 1936.

increase in the output of potassium in the urine. Schittenhelm, Erhardt and Warnat [43] demonstrated the ability of the liver to withhold potassium, thus preventing a systemic rise, and Marenzi and Gerschman [44] pointed out the possibility of increased storage of potassium in the red blood cells.

With these points in mind, it is hypothesized that, as a result of the insulin hypoglycemia, with its so-called cellular anoxia, which leads to an increase in the permeability of the cell membrane and a decrease in its selectivity, there are an outpouring of potassium from the cell and a shifting of sodium from the extracellular spaces to the cell, and with this shift in sodium there is an accompanying aliquot of water. If the cellular anoxia continues or increases, there are, we believe, a progressive loss of potassium and dilution of the cell contents with incoming water to an irreversible point, after which there is complete loss of the functional, and frequently the structural, integrity of the cell. In such an event, the prognosis, as well as the clinical picture, depends on the number of cells involved and their location. If such an episode is survived by the organism, the loss of water from cells damaged by this hydration would explain the dark-staining, pyknotic, small, shrunken cells mentioned previously in the pathologic description.

Viewed from the standpoint of the cell unit, or as a whole, the brain is a protoplasmic colloidal gel. In any colloidal system variations in the nature and functions of the interfaces bring about variations in the reaction and character of the system. Thus, the change in ion concentration produced by the change in blood electrolytes or by the cellular anoxia or by both is effective in changing the permeability of the cell surface, since the integrity of the cell surface is dependent on the homeostasis established between intracellular and extracellular ions. Chemicals in combination or singly are physiologically and chemically impotent when they are present within the colloidal structure of a cell. All colloids are characterized by activity occurring on the surface of the colloid. Consequently, that material which is impotent when bound in a cell becomes highly active when present on the cell surface, viz., in the intercellular fluid, because intercellular fluid bathes cell interfaces. This is true of the potassium content of the normal cell, but when there is such a change in the cell surface as that previously described, the potassium liberated into the surrounding medium becomes as highly potent in its ability to change the original functional and physical status of the cell as it was impotent to do so when bound in the original colloid. It follows that the amount of potassium liberated may determine the extent of the change. While there is an optimal ratio of dispersed phase to continuous phase for colloidal matter at which the stability is maximum, there is, nevertheless, a range of physical variation within the limits of which the colloid may be altered and the function commensurately disturbed without irreversible changes necessarily being produced. However, a point can be reached at which the changes become irreversible. Both structure and function are then irrevocably disturbed.

The physical phases through which the gel passes range from agglutination of the colloidal particles to the formation of larger micelles and, finally, to precipitation of such conglomerates, with subsequent loss of total bulk and typical structure and the formation of vacuoles within the remnant of the original structure. This process would explain the pathologic picture seen in brain damaged by insulin therapy. In the whole brain, minimal changes, although they may proceed to the point of irreversibility, need not necessarily change the total structure or the total function. It follows that the accumulative amount of such irreversible changes will determine the pathologic picture.

CONCLUSIONS

An evaluation of the data in 51 cases of prolonged coma occurring in 38 patients during the course of insulin shock therapy leads to the assumption that some factor within the patients themselves, rather than the technic of treatment alone, was responsible for these prolonged comas.

A method suggested for the management of this complication is based on the experience gained in treating these patients, and the physiologic soundness of this method rests on a presented explanation of the mechanism of this complication.

With emphasis on the dynamic nature of the action of insulin shock and insulin shock stupor progressing to the irreversible phase of prolonged coma and with free use of the contemporary literature, an attempt is made to explain the varying pathologic pictures in the light of progressive cellular hydration.

111 North Forty-Ninth Street.

43. Schittenhelm, A.; Erhardt, W., and Warnat, K.: Ueber den Kalium- und Calciumgehalt von Blut und Organen des Kaninchens und des Hundes und seine Veränderungen beim sensibilisierten und anaphylaktischen Tier, Ztschr. f. d. ges. exper. Med. **58**:662, 1928.

44. Marenzi, A. D., and Gerschman, R.: Adrenalina y potasio sanguíneo, Rev. Soc. argent. de biol. **12**:424, 1936.

FATAL CIRCULATORY FAILURE CAUSED BY ELECTRIC SHOCK THERAPY

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At present convulsive therapy is widely used for certain psychoses, with beneficial results in a sufficiently large number of cases to insure its continuance. Recently the passage of an electric current through the frontal lobes of the brain has come to be the most generally favored method for the production of therapeutic convulsions.

That this type of therapy, regardless of the manner in which the convulsions are induced, may result in death from circulatory failure should not be ignored. There are probably at least two mechanisms by which electrically induced convulsions precipitate circulatory failure. One is by the overload imposed on the heart by the muscular exertion of the convulsion itself; the other is by the extent to which the current affects the central cardioregulatory and vasomotor centers.

Whether or not these circulatory disturbances are survived probably depends in part on the irritability of the cardioregulatory and vasomotor centers and in part on the functional reserve of the heart. It is the purpose of this communication to call attention to the importance of the latter and to emphasize the desirability of determining as far as possible the irritability and functional reserve of the patient's cardiovascular system before he is subjected to convulsive therapy.

Although the electric shock treatment may be tolerated by a person having a normal cardiovascular system without ill effects, it should be recognized that the additional burden placed on an already diseased heart may lead to rapid decompensation and failure. Three recent cases in which acute circulatory collapse and death were apparently the result of such an occurrence were judged to be of sufficient interest in this connection to justify their publication.

REPORT OF CASES

CASE 1.—A white man aged 61 had exhibited increasing depression for two years, since the suicide of his wife. He expressed numerous paranoid ideas and stated the belief that his food was poisoned and that he was to be prosecuted for murdering his wife. After institutionalization in a private hospital for mental disease, he appeared extremely depressed and retarded and exhibited a delusional system of paranoid nature. The diagnosis was manic-depressive psychosis—depressed type.

No outstanding abnormalities were disclosed by the physical examination. The heart did not appear enlarged on percussion, and the rate was regular. A minor systolic murmur was heard at the apex and over the aortic area. The blood pressure was 156 systolic and 90 diastolic. The blood count and urinalysis revealed nothing abnormal.

The course of his illness in the hospital was without essential change or improvement, and the electric shock therapy was administered at three day intervals. The first seven of these treatments were not accompanied by any difficulty. Prior to the eighth treatment examination disclosed a temperature of 98.6 F., a regular pulse with a rate of 84 per minute and a blood pressure of 140 systolic and 88 diastolic. A dose of 450 milliamperes for a duration of five-tenths second was administered. The response to the application of the shock was a tonic convulsion of moderate degree, which then passed over into the clonic phase. The total period of the convulsion was thirty seconds. There was only a few seconds of apnea. Ninety seconds after the passage of the electric current the pulse was weak, with a rate of 120 per minute. The face was pale, and breathing was irregular. An ampule of nikethamide was administered; the patient stirred restlessly and muttered incoherently, appearing somewhat improved. Ten minutes after the electric shock his breathing again became irregular, and artificial respiration was begun. No pulse was detectable two minutes later.

Gross Pathologic Examination.—The body was well nourished and well developed. The heart was the seat of an eccentric hypertrophy and weighed 525 Gm. The coronary arteries were tortuous and rigid. Multiple sectioning revealed that they were the site of an extensive obliterating sclerosis (fig. 1). In the lumen of the right coronary artery 3 cm. from the orifice there was a brown mass, 1 cm. long, with two small central channels. Distal and proximal to this mass the vessel was the site of arteriosclerosis with chiefly concentric formation and considerable calcification, but the lumen was widely patent. The left coronary artery showed a segment about 1 to 2 mm. in length in which the lumen was represented by an extremely small, eccentrically placed opening in what appeared to be an almost completely depigmented, organized thrombus.

In the left anterior descending coronary artery, at a point beginning 1 cm. from its origin, there was a segment 2 to 3 cm. in length in which an eccentric subintimal hyaline plaque produced a lumen of pinpoint dimensions. A similar condition was encountered in the left circumflex artery over a segment of 2 cm., the plaque beginning at a point 1.5 cm. from the origin of the vessel.

Section of the heart revealed an area of myocardial thinning, 4 cm. in diameter, in the posterior wall of

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the left ventricle. The lesion was soft, varied from dark red to reddish brown and extended into the posterior portion of the interventricular septum. From this area gross focal myocardial scarring continued forward into the lower half of the anterior two thirds of the septum.

The endocardium throughout both ventricles was thickened, and the columnae carneae and pectinate muscles were flattened. There appeared to be moderate dilatation of the ring of the mitral valve, and several small fatty and hyaline atherosclerotic patches presented on the atrial surface of the valve. The other valves showed no significant abnormalities.

In the brain moderate sclerotic changes involved the arteries and the arterioles. The arterial lesions were of the usual atheromatous type and were nowhere severe. The arteriolar lesions consisted chiefly of hyaline thickening and were seen best in the cortex. The distribution of these lesions was patchy. Occasional relatively acellular areas were encountered in the cortex. There was minor perivascular gliosis in relation to the course of some of the larger blood vessels in and beneath the cortex. The nuclei of the cranial nerves and the cortical parenchyma presented no significant abnormality. In the white matter there were moderate hyperemia and occasional petechiae.

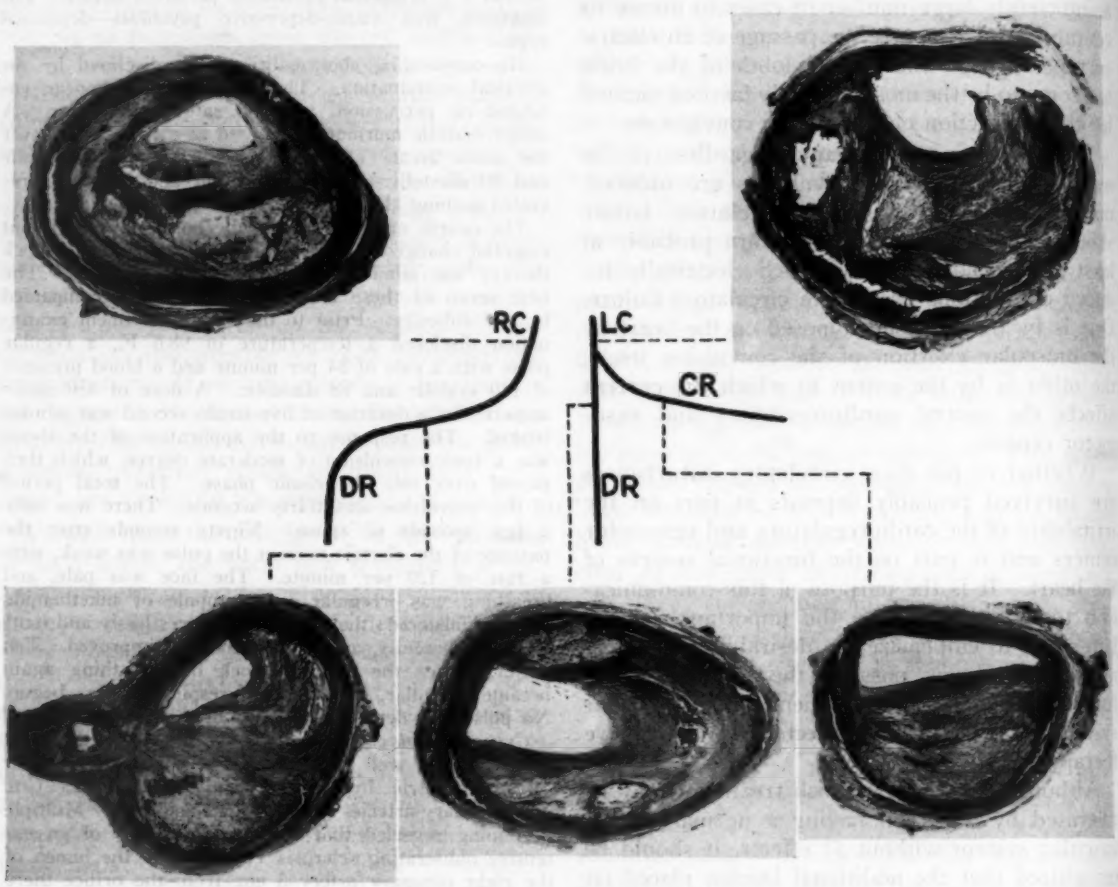

Fig. 1 (case 1).—Severe generalized coronary arteriosclerosis. *LC* indicates the left coronary artery; *RC*, the right coronary artery; *CR*, the circumflex ramus, and *DR*, the descending ramus.

The brain was symmetric and hyperemic and weighed 1,300 Gm. The leptomeninges showed slight diffuse thickening throughout. No gross abnormalities were observed on section of the brain after fixation in a dilute solution of formaldehyde U. S. P. The cerebral arteries showed rare fatty and hyaline subintimal plaques.

The other viscera showed no significant abnormalities except for severe passive hyperemia.

Microscopic Examination.—A section from the posterior wall of the left ventricle of the heart revealed a two to three week old infarct, in which the myocardium had been replaced by organizing granulation tissue containing hemosiderin-laden histiocytes. Other sections showed replacement fibrosis of the myocardium, with irregular scarring of myocardial bundles of both perivascular and interstitial distribution.

The kidney showed moderate arterial and arteriolar sclerosis. Some of the glomeruli were replaced by collagen.

Diagnosis.—The principal pathologic diagnoses were: (1) extensive obliterating coronary arteriosclerosis; (2) recent myocardial infarct; (3) replacement fibrosis of the myocardium; (4) hypertrophy and dilatation of the heart; (5) arterial and arteriolar nephrosclerosis, of moderate degree; (6) moderate cerebral arteriosclerosis, and (7) severe passive hyperemia of the viscera.

It was evident that death was attributable to acute heart failure, contributed to by arteriosclerotic heart disease and precipitated by electrically induced convulsions.

Case 2.—A white man aged 70, a retired physician, had at the age of 59 been treated for angina on

exertion, at which time a diagnosis of coronary heart disease was made. A year before his death he became depressed and worried and complained of pain in the head and back. Six months later he suddenly collapsed, was semiconscious for several hours and remained in bed for several weeks. Subsequently he became forgetful and absent minded, lost interest and initiative, ate and slept poorly and began to take opiates. Two months before his death he attempted suicide by the ingestion of a barbiturate. He was studied subsequently in a general hospital, where a diagnosis of hypertensive vascular disease, cerebral thrombosis, coronary thrombosis (old) with bundle branch block, hypertrophic arthritis, drug addiction and cerebral arteriosclerosis was made. An electrocardiogram was interpreted as showing "evidence of coronary heart disease and left frontal bundle branch block" (fig. 2).

He was admitted directly to a private institution for mental diseases, where his condition remained relatively unchanged. He was extremely restless and depressed, said he felt that he was going to lose his mind and expressed suicidal ideas. A diagnosis of agitated depression was made. Electrotherapy was decided on, the risk of the procedure being made clear to relatives in view of the known heart disease. The overactivity of the patient also constituted a cardiac risk, and under the circumstances it was decided that electrotherapy was justified.

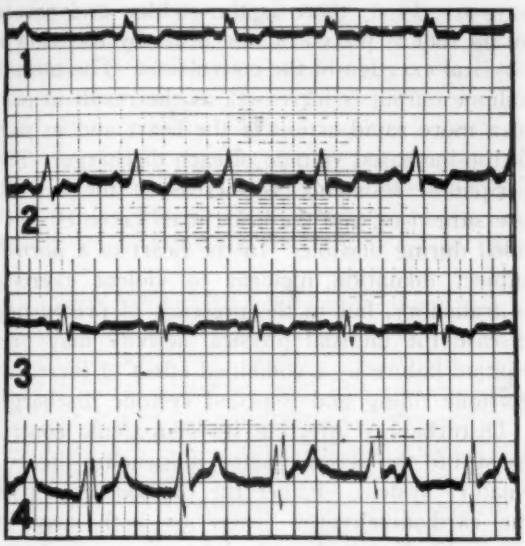

Fig. 2 (case 2).—Electrocardiogram, showing a well defined bundle branch block of the left type, with normal rhythm except for one ventricular beat in lead I (interpretation by Dr. Paul D. White).

Five treatments were given at approximately three day intervals, with no untoward results. The mental condition did not improve. The final treatment consisted of a dose of 400 milliamperes administered for five-tenths second, before which the systolic blood pressure was 158 mm. A convulsion lasting forty-eight seconds occurred immediately, after which the systolic pressure rose to 198 mm. There was no significant period of apnea. After a few minutes the pulse became thready and weak; pulmonary edema developed, and the patient was pronounced dead twelve minutes after the beginning of the treatment.

Gross Pathologic Examination.—The body was well developed and well nourished.

The heart was the seat of severe eccentric hypertrophy and weighed 585 Gm. after fixation in dilute solution of formaldehyde U. S. P. The myocardium of the anterior wall of the left ventricle and the contiguous portion of the interventricular septum, 3.8 cm. from the apex, was replaced by fibrous tissue in an area measuring 2.5 cm. in diameter. The descending ramus of the left coronary artery was the seat of segmental obstructing sclerosis. The circumflex branch was comparatively large, whereas the right coronary artery was small. These arteries showed less severe arteriosclerosis than did the descending ramus of the left coronary artery.

There was severe intimal sclerosis of the aorta.

The brain was symmetric and hyperemic and weighed 1,350 Gm. after fixation in dilute solution of formaldehyde U. S. P. The arteries comprising the circle of Willis and their main branches were the site of isolated subintimal fatty and hyaline atherosclerotic plaques, producing minor eccentric narrowing of the lumen. Frontal section revealed two cystic infarcts, less than 0.4 inch (1 cm.) in diameter, in the right lenticular nucleus.

The kidneys weighed 260 Gm., and their surfaces were finely granular and red. The cortices were irregularly atrophic and red, and the architecture was indistinct. The interarcuate arteries were thickened.

Microscopic Examination.—The heart showed a healed myocardial infarct, with relatively acellular scar tissue replacing muscle. There was generalized interstitial fibrosis of moderate degree.

As in case 1, the brain was the seat of moderate sclerotic changes involving both arteries and arterioles. There were occasional acellular areas without reaction throughout the cortex, and myelin stains showed slight rarefaction about cortical vessels. In addition to the old infarcts in the lenticular nuclei, which were bordered by a dense glial zone, multiple small, recent cortical infarcts were present in all lobes. These lesions consisted of proliferating capillaries, astrocytes and a few fibroblasts, replacing necrotic brain tissue. Numerous compound granular corpuscles were present. Some of the vessels in the white matter were surrounded by minor hemorrhages. The nuclei of the cranial nerves and the cortical cells appeared normal.

In the kidneys there was arterial and arteriolar sclerosis, and many of the glomeruli were replaced by collagen.

Diagnosis.—The significant anatomic diagnoses were: (1) obliterating coronary arteriosclerosis; (2) ancient myocardial infarct; (3) replacement fibrosis of the myocardium; (4) hypertrophy and dilatation of the heart; (5) arterial and arteriolar nephrosclerosis; (6) cerebral arteriosclerosis; (7) old healed infarcts of the right lenticular nucleus; (8) recent small cortical infarcts, and (9) severe passive hyperemia of the viscera.

It was thought that death could be attributed to acute heart failure, for which severe coronary arteriosclerosis was a predisposing factor and the electric shock treatment the precipitating agent.

CASE 3.—A white man aged 23 had been mentally ill for several years. He had been institutionalized over most of this period, the diagnosis being dementia precox. During these previous admissions he had received both metrazol and insulin shock therapy.

During his last admission he was given a course of eight daily electric shock treatments. The mental condition remained unchanged. Two months later a second series of treatments was begun. The first seven were unaccompanied by any apparent complication. Before the eighth, and final, treatment he appeared normal physically. A dose of 800 milliamperes for a duration

of three-tenths second was administered, and a convulsive reaction was obtained, similar in all respects to the others. Afterward he appeared as usual and went to the cafeteria for his lunch and supper. He became restless in the early evening and was observed to go to the bathroom frequently. At midnight he appeared dyspneic and on examination showed evidence of pulmonary edema. The pulse and respiratory rates were 120 and 52 per minute respectively. The patient was transferred to a medical ward in collapse and died shortly thereafter.

Gross Pathologic Examination.—The body was well developed and well nourished. There was moderate pitting edema of the ankles and sacrum. Each pleural cavity contained approximately 400 cc. of a serous, light yellow fluid, and about 500 cc. of a similar fluid was present in the abdominal cavity. The lungs were the seat of severe edema and moderate hyperemia. The heart was acutely dilated and weighed 305 Gm. The myocardium was flabby, more friable than usual and a cloudy gray-red. The valves and coronary arteries were normal. The kidneys together weighed 350 Gm. The capsules were thin and stripped easily from the smooth red surfaces. The cortex of each kidney was of average thickness and was gray-red, with the striations partially obscured. The medulla was hyperemic. None of the other viscera, including the brain, showed significant changes except for severe passive hyperemia.

Microscopic Examination.—Sections of the kidney showed enlarged, avascular glomeruli, with an increased number of nuclei. Generally, the capillaries were completely occluded by endothelial cells and, to a lesser degree, by polymorphonuclear leukocytes. In some glomeruli there was focal necrosis of the cells of the loops. Azocarmine stains showed intralobular thickening of the capillary basement membrane. Granular albuminous detritus was observed in the tubules and in the subcapsular space of the glomeruli. There was no evidence of tubular atrophy. The epithelium of the tubules was the site of cloudy swelling and contained a minimal number of fat droplets. There was moderate interstitial edema.

In the heart the myocardium showed changes ranging from swelling and loss of transverse striations of the muscle fibers to small focal areas of granular and hyaline necrosis. These small and irregularly placed foci were usually related to a cellular infiltrate, consisting of histiocytes, lymphocytes, plasma cells and neutrophilic leukocytes. Occasionally the lesions included a small amount of loosely arranged basophilic collagen fibrils. There was only a minimal degree of fatty degeneration.

None of the other viscera, including the central nervous system, showed significant abnormalities except for the presence of severe passive hyperemia. Occasional petechiae were observed in the white matter of the brain.

Diagnosis.—The essential anatomic diagnoses were: (1) acute diffuse nonsuppurative glomerulonephritis; (2) acute focal nonsuppurative myocarditis; (3) acute pulmonary edema; (4) peripheral edema of the ankles and sacrum; (5) hydrothorax and ascites, and (6) acute passive hyperemia of the viscera.

Death was considered the result of rapidly progressing heart failure.

COMMENT

The electrically induced convulsion begins with a violent start, which is simultaneous with the completion of the electric circuit. Whether or not the current spreads through the entire brain is not known. Alexander [1] stated that the electric current passes from one electrode to the other by the most direct path without deflection by structural variations of the intervening tissue. In the case of electric shock the electrodes are placed over the temples, and the path of the current is through the frontal poles.

Within a few seconds after the actual application of current, and presumably as a result of mass cerebral irritation, the convulsion begins. The initial violent tonic seizure is followed by a clonic phase, the entire episode lasting about thirty to forty-five seconds. The period of recovery is variable, but usually the subject becomes conscious within less than thirty minutes, and ordinarily within five to ten minutes.

As a result of two major factors, electric shock may have profound effects on the circulatory system. First, there is the sudden and severe strain that is placed on the heart by the violent physical exertion of the convulsion. The minute volume output is increased, as the result in part of a more rapid action of the heart and in part of the increased volume of each discharge. The peripheral resistance is increased; the arterial pressure rises, and the heart itself becomes overfilled during diastole. In the heart of a normal subject dilatation incident to violent exercise is transitory, but in the presence of preexisting disease the unusual physical activity may precipitate failure by a combined effect of increased diastolic filling and impeded systolic discharge.

Disturbances affecting its neurogenic control constitute the second factor influencing the circulatory system. Either the cardiodepressor or the cardioaccelerator center or both may be affected. From clinical observation it appears that disturbances of the cardiodepressor center occur with greater frequency, or at least assume the dominant position. Thus, reflex vagocardiac inhibition, with slowing or stopping of the heart, reflex systemic vasodilatation, with its accompanying severe fall in blood pressure, or a combination of the two mechanisms may occur.

Epstein [2] observed a notable decrease in the blood pressure and the pulse rate immediately after a convulsion, the systolic pressure dropping from 160 to 80 mm. Almost always the rhythm of the heart is disturbed. While such changes are usually minor, they may be pronounced, even in physically normal patients. Postconvulsive asystole has been reported (Bellet and associ-

1. Alexander, L.: Electrical Injuries of the Nervous System, J. Nerv. & Ment. Dis. **94**:622, 1941.

2. Epstein, J.: Electric Shock Therapy in the Psychoses, J. Nerv. & Ment. Dis. **98**:115, 1943.

ates [3]). It seems altogether possible that such a severe vagotonic reaction might easily predispose to the development of fatal acute circulatory failure in a heart which is the seat of preexisting disease.

In subjects with presumably a hypersensitive nervous control of the heart and blood vessels, it is known that reflex circulatory failure is occasionally caused by apparently minor trauma. Injury to a so-called trigger region, such as a blow over the solar plexus or to the testes, dilatation of the rectum or even a needle puncture of the pleura, often results in syncope, and occasionally in instantaneous death. Weiss and Baker,[4] in a clinical study of irritability of the carotid sinus, observed great individual variations. In some patients even the pressure of a tight collar band was sufficient to cause unconsciousness. If electrotherapy were given to patients with such hyperirritability, it is possible that the consequent mass stimulation of the cerebrum would prove fatal even without preexisting cardiovascular disease. If hypersensitivity of the carotid sinus could be taken to indicate a similar sensitivity of the cardioregulatory and vasomotor centers, information of value in the selection of candidates for electric shock treatment might be obtained by determining the irritability of the sinus.

It is more difficult to demonstrate adequately a sympathetic effect incident to stimulation of the cardioacceleratory center. Although increases in blood pressure, heart rate and cardiac output are frequently encountered subsequent to the convulsions, it is questionable whether the action should be attributed to primary neurogenic stimulation or to a secondary effect of the violent physical exertion of the convulsion. The fact that changes in the diameter of the pupils sometimes occur during these pressor episodes makes it possible, in such instances at least, that a more widespread sympatheticotonic reaction takes place than can reasonably be accounted for on the basis of muscular activity alone.

A causal relationship between electric shock and death seems clearly established in the first 2 cases. The patients were in the seventh and eighth decades of life respectively, and because of advanced coronary arteriosclerosis a condition of diminished cardiac reserve unquestionably existed. In neither of the cases was the convulsion unusual, and no significant vagotonic reaction occurred. Immediately after the convulsion the pulse rate in each case was considerably increased, and in the first case a blood pressure reading revealed an elevation of the preconvulsive systolic level to 198 mm. For three or four minutes the general condition appeared satisfactory; then, however, there was evidence of increasingly severe circulatory collapse, death occurring within ten minutes. It does not appear that in either of these cases the significant factor in the causation of death was neurogenic. No valid reason obtains for postulating that death was anything but the result of inability of a diseased heart to recover from the strain imposed by the unusual physical exertion of the convulsion itself. While fatal circulatory collapse occurs with coronary heart disease without significant physical exertion, it is probable that the preceding pressor episode precipitated heart failure.

The existence of a causal relation between treatment and death in the third case is less clear than in the first 2 cases. The patient, a man of 23, had acute glomerulonephritis with associated acute myocarditis. From the histologic appearance of the kidneys the nephritis was of several days' duration. The myocarditis was acute and in all probability was produced by the same agent that caused the nephritis. The mode of death was that of acute circulatory collapse, the postmortem manifestations of which were acute cardiac dilatation, pulmonary edema and visceral hyperemia. The peripheral edema, ascites and hydrothorax could with some reason be attributed to circulatory failure rather than to the nephritis itself.

Whether death would have occurred in this case without the series of eight electric shock treatments given at daily intervals is questionable. It must be remembered that a twelve hour period of apparent well-being intervened between the last treatment and the time when heart failure was first recognized. Circulatory failure as a complication of acute glomerulonephritis is not infrequent, and it is probably the commonest cause of death in cases in which the disease proves fatal during the early weeks of its course. On the other hand, there remains the distinct possibility that electrotherapy acted as a complicating factor by introducing further strain on the already overtaxed heart. With the treatments given at daily intervals, it might be further speculated that the effect was cumulative.

A review of the literature reveals 6 other cases in which death apparently was due to a fatal cardiac complication incident to electric shock therapy, a surprisingly small number in view of the present day widespread use of the treatment. The ages of the patients varied from 50 to 75 years, and autopsy was performed in 4 of the 6

3. Bellet, S.; Kershbaum, A., and Furst, W.: The Electrocardiogram During Electric Shock Treatment of Mental Disorders, Am. J. M. Sc. **201**:167, 1941.

4. Weiss, S., and Baker, J. P.: Carotid Sinus Reflex in Health and Disease, Medicine **12**:297, 1933.

cases. Ebaugh and associates [5] reported 2 of these 4 cases and cited an additional case. In 2 of these 3 cases there was preexisting arteriosclerotic heart disease. In the third case the patient, who had previously experienced respiratory difficulty in preceding treatments, failed to recover from the apnea following the convulsion. Pathologic examination failed to reveal an adequate cause for the sudden death. It seems quite likely that the fatal mechanism was a severe vagotonic reaction with cessation of cardiac and respiratory function. The fourth case in which autopsy was done is mentioned by Levy [6]; although the details are not clear, it is evident that death in this case, also, was of so-called vagotonic origin.

Reports concerning the effect of electric shock therapy on the central nervous system are conflicting. In experiments with electric shock Alpers and Hughes,[7] using cats, and Heilbrunn and Weil,[8] using rabbits and rats, observed focal leptomeningeal and perivascular hemorrhage. Neubuerger and associates,[9] in similar experiments on dogs, observed minor parenchymal alterations. In the brains of 2 patients who died several months after the last electrically induced convulsion, Alpers and Hughes [10] observed old and more recent perivascular hemorrhages, which were usually related to circumscribed areas of rarefaction and minor gliosis. These alterations were attributed to the treatment.

On the other hand, Globus, van Harreveld and Wiersma [11] were unable to detect significant histologic alterations in the brains of dogs which were subjected to shock with an electric current of an amperage equivalent to the dose for human subjects for as much as thirty seconds. Likewise, in the 3 cases reported in this paper no pathologic abnormalities were observed in the brain which could be considered directly attributable to the treatment. Scattered perivascular hemorrhages were seen, but it was felt that they were incident to the acute circulatory collapse rather than to the treatment itself. It has been my experience that such lesions are of common occurrence in cases of death associated with any significant degree of agonal anoxemia. The histologic alterations in the brain in the first 2 cases, characterized chiefly by hyaline thickening of the arterioles, minor perivascular rarefaction and gliosis and minor focal cortical atrophy, were consistent with a diagnosis of cerebral arteriosclerosis.

It is not the purpose of this paper to discuss the merits of convulsive shock therapy or the relative efficacy of the insulin, metrazol and electric shock methods. From the standpoint of ease of administration the electric shock method has certain advantages. The elimination of the intravenous route rules out such possible complications as infection, thrombosis and pulmonary embolism. The incidence of fatalities with electric shock therapy is low, and in a recent survey by Kolb and Vogel [12] the death rate was only 0.5 per thousand in 7,200 cases, as compared with 1 per thousand for the metrazol method and 6 per thousand for insulin treatment. The 3 deaths reported here occurred among 2,500 patients in state, private and veterans institutions for mental diseases in Massachusetts who had been treated by the electric shock method, with a mortality rate of 1.2 per thousand.

In the selection of patients for treatment two main problems present themselves. The first is whether or not the candidate's general physical condition warrants the use of the therapeutic procedure. The treatment of patients with significant cardiovascular disease, particularly if they are in the older age group, should be considered with reservation, if at all. Similarly, caution should be observed with persons in whom there is reason to expect the presence of hypersensitivity of the cardioregulatory and vasomotor mechanisms.

The over-all problem in the selection of patients is, however, a more inclusive one than that based merely on the physical condition. While undoubtedly a small group will be found for whom treatment is definitely contraindicated by reason of important heart disease, it is more than likely that a much larger group will be encountered who present less definite contraindications for treatment. One must consider

5. Ebaugh, F. G.; Barnacle, C. H., and Neubuerger, K. T.: Fatalities Following Electric Convulsive Therapy: Report of Two Cases with Autopsy, Arch. Neurol. & Psychiat. **49**:107 (Jan.) 1943.

6. Levy, N., in discussion on Heilbrunn and Weil,[8] p. 928.

7. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat. **47**:385 (March) 1942.

8. Heilbrunn, A., and Weil, A.: Pathologic Changes in the Central Nervous System in Experimental Electric Shock, Arch. Neurol. & Psychiat. **47**:918 (June) 1942.

9. Neubuerger, K. T.; Whitehead, R. W.; Rutledge, E. K., and Ebaugh, F. G.: Pathologic Changes in the Brains of Dogs Given Repeated Electrical Shocks, Am. J. M. Sc. **204**:381, 1942.

10. Alpers, B. J., and Hughes, J.: Brain Changes in Electrically Induced Convulsions in the Human, J. Neuropath. & Exper. Neurol. **1**:173, 1942.

11. Globus, J. H.; van Harreveld, A., and Wiersma, C. A. G.: The Influence of Electric Current Application on the Structure of the Brain of Dogs, J. Neuropath. & Exper. Neurol. **2**:263, 1943.

12. Kolb, L., and Vogel, V. H.: The Use of Shock Therapy in Three Hundred and Five Mental Hospitals, Am. J. Psychiat. **99**:90, 1942.

two factors in deciding whether the risk of the treatment is greater than the risk of withholding a potentially beneficial procedure from such a person. The first is the apparently extremely low mortality rate in all series. The second is the question whether or not the psychosis, with its accompaniment of emotional upset, agitation and restlessness, might not do more to aggravate a preexisting physical abnormality than would the treatment itself. In the final analysis, it is the psychiatrist who, after critically evaluating all the pertinent data, must make the decision.

CONCLUSIONS

There are probably at least two mechanisms by which fatal circulatory failure may be precipitated by electric shock therapy. In the first the acute cardiac dilatation and failure are caused by the tremendous muscular exertion of the convulsion. The likelihood of such an occurrence undoubtedly bears a direct relation to the severity of already existing heart disease. In the second the circulatory failure may occur without recognizable heart disease, and possibly results from the electrical stimulation of hyperexcitable central cardioregulatory or vasomotor centers. The existence of this mechanism should be regarded as hypothetic rather than proved.

Of 3 patients who died of circulatory failure after electric shock treatment, 2 had advanced arteriosclerotic heart disease and the other acute myocarditis.

Electric shock therapy of persons with heart disease or of persons suspected of unusual susceptibility to disturbances of the central vasomotor or the central cardiac centers should not be undertaken without full realization of the potential hazard.

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RACIAL AND SEXUAL INCIDENCE OF PRIMARY INTRACRANIAL TUMORS

STATISTICAL STUDY OF ONE HUNDRED AND THIRTY-THREE CASES VERIFIED BY AUTOPSY

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The racial incidence of primary intracranial tumors has received little attention in the literature. Since more than one-half the necropsies at Charity Hospital, New Orleans, have been carried out on Negroes, it seemed that the study of autopsy material from this hospital might be instructive.

MATERIAL AND METHOD

This study was based on the records of 10,112 consecutive autopsies (1929 to 1942 inclusive) performed on patients between the ages of 1 month and 70 years, the age range of patients with intracranial tumors in this series. In addition, the records of 649 studies of brains made between January 1940 and July 1943 were reviewed and the results of the survey correlated with the facts obtained from the study of the total number of autopsies. The second series was used as a control to indicate any abnormal distribution of brains among the various racial and sexual groups. There were slightly more brains of Negro females and slightly fewer of white males (table 1) than was to be expected. This distribution made the total number of brains of white patients and the total number of brains of male patients slightly less than was to be expected, and the total number of brains of female patients slightly more than was to be expected. The extent of these variations was not sufficient, however, to explain the differences in the distribution of primary intracranial tumors between the Negro and the white race and between the male and the female sex.

The method of analysis has been described by Fisher.[1] The expected figure (m) is obtained for any single figure by multiplying the horizontal total by the vertical total and dividing the result by the total number of cases. The difference between the expected and the actual figure is x. The deviation of the actual from the expected value is obtained by the formula x^2/m. This deviation is significant when the number so obtained is greater than 1.

RESULTS

In the series of 10,112 autopsies, a total of 133 primary intracranial tumors was observed. Of this number, 45 occurred in members of the Negro race and 88 in members of the white race (table 2). Stated in another way, 1 out of 47 white patients on whom necropsy was performed had a primary intracranial tumor, while only 1 out of every 132 of the Negro patients had such a tumor. These figures become more significant when one remembers that 1,782 more autopsies were carried out on Negro patients than on white patients.

There was no apparent difference in the sexual distribution of primary intracranial tumors as a whole, 79 occurring in males and 54 in females. These figures closely approximate the expected values. However, when the sexes of the two races are considered separately, a sexual difference becomes apparent. Although nearly twice as many autopsies were performed on white males as on white females, only 46 primary intracranial tumors occurred in the former and 42 in the latter. When this incidence is corrected, the frequency of primary intracranial tumors in white females was nearly twice that in white males. Almost the exact reverse held true for Negro males and Negro females, the incidence being nearly twice as great for the males.

Of the 133 primary intracranial tumors, 80 were gliomas. This type of tumor also was much more frequent in members of the white race. One out of every 77 white patients with a primary intracranial tumor, as compared with 1 out of every 229 Negro patients, had a glioma.

The distribution of gliomas between the two sexes for the entire series was approximately that to be expected. However, the frequency was higher, both in actual numbers and in the percentage of autopsies among the white females (1 glioma in every 59 white females) and the white males (1 glioma in every 91 white males).

1. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, Oliver & Boyd, Ltd., 1938.

By comparison, in 1 out of every 186 Negro males and in 1 out of every 344 Negro females the primary intracranial tumor was a glioma.

The gliomas were further divided into the various subtypes (table 3). Except for the cases of glioblastoma multiforme and astrocytoma the number of instances of each type was insufficient to be of statistical value. The incidence of the glioblastoma multiforme (in 18 white persons and 6 Negroes) and of the astrocytoma (in 21 white persons and 4 Negroes) again emphasized the greater frequency of gliomas in the white race. Division of the total number of cases of gliomas into those of the adult and those of the primitive type did not reveal predominance in either race or sex.

TABLE 1.—*Ratio of Brains Examined to Autopsy Records Studied*

		Negro Males	Negro Females	White Males	White Females	Total No. of Negroes	Total No. of White Persons	Total No. of Males	Total No. of Females	Total Series
Total series of autopsies (1929-1942)	Actual number	3,537	2,410	2,739	1,426	5,947	4,165	6,276	3,836	10,112
	Expected number	3,530	2,433	2,716	1,432	5,964	4,139	6,246	3,866	
	x^2/m	0.014	0.213	0.190	0.250	0.05	0.16	0.14	0.23	
Total number of brains examined over 2½ year period	Actual number	220	180	151	98	400	249	371	278	649
	Expected number	226	156	174	91	383	266	400	248	
	x^2/m	0.159	3.69	3.04	0.54	0.76	1.09	2.10	3.63	
Total		3,757	2,590	2,890	1,534	6,347	4,414	6,647	4,114	10,761

TABLE 2.—*Racial and Sexual Incidence of Primary Intracranial Tumors*

	Negro Males	Negro Females	White Males	White Females	Total No. in Negroes	Total No. in White Persons	Total No. in Males	Total No. in Females	Total Series
Total number of gliomas	19	7	30	24	26	54	49	31	80
Expected number	(27.92)	(19.04)	(21.73)	(11.38)	(46.88)	(33.11)	(49.71)	(30.35)	
x^2/m	(1.72)	(7.66)	(3.10)	(13.99)	(9.30)	(13.18)	(0.01)	(0.01)	
Ratio	1:186	1:344	1:91	1:59	1:229	1:77	1:128	1:123	1:126
Total number of meningiomas	5	2	9	12	7	21	14	14	28
Expected number	(9.78)	(6.66)	(7.58)	(3.97)	(16.44)	(11.55)	(17.36)	(10.63)	
x^2/m	(2.34)	(3.26)	(0.27)	(16.24)	(5.42)	(7.73)	(0.65)	(1.06)	
Ratio	1:707	1:1,205	1:304	1:119	1:849	1:198	1:463	1:274	1:361
Other varieties	9	3	7	6	12	13	16	9	25
Expected number	(9.73)	(5.95)	(6.77)	(3.53)	(14.69)	(10.30)	(15.51)	(9.48)	
x^2/m	(0.05)	(1.46)	(0.00)	(1.73)	(0.48)	(0.70)	(0.01)	(0.02)	
Ratio	1:393	1:803	1:391	1:238	1:541	1:379	1:448	1:479	1:464
Total number of tumors	33	12	46	42	45	88	79	54	133
Expected number	(47.42)	(31.44)	(36.15)	(19.06)	(77.78)	(55.21)	(82.50)	(50.49)	
x^2/m	(4.38)	(12.02)	(2.68)	(27.64)	(13.82)	(19.47)	(0.14)	(0.24)	
Ratio	1:107	1:201	1:60	1:34	1:132	1:47	1:79	1:71	1:76
Total number of autopsies	3,537	2,410	2,739	1,426	5,947	4,165	6,276	3,836	10,112

TABLE 3.—*Racial and Sexual Incidence of Intracranial Gliomas*

	Negro Males	Negro Females	White Males	White Females	Total No. in Negroes	Total No. in White Persons	Total No. in Males	Total No. in Females	Total Series
Primitive types									
1. Medulloblastoma	2	2	0	2	4	2	2	4	6
2. Glioblastoma multiforme	5	1	8	10	6	18	13	11	24
3. Astroblastoma	0	1	2	0	1	2	2	1	3
Total	7	4	10	12	11	22	17	16	33
Adult types									
4. Astrocytoma	4	0	12	9	4	21	16	9	25
5. Spongioblastoma polare	1	0	1	0	1	1	2	0	2
6. Ependymoma	2	1	2	1	3	3	4	2	6
7. Pinealoma	2	1	1	0	3	1	3	1	4
8. Oligodendroglioma	1	0	1	0	1	1	2	0	2
Total	10	2	17	10	12	27	27	12	39
Glioma, unclassified	2	1	3	2	3	5	5	3	8
Total of all forms	19	7	30	24	26	54	49	31	80

The racial difference in the distribution of meningiomas was striking. Three white persons had such a tumor for every Negro. This tumor was slightly more frequent in the females as a whole. This was especially apparent in the white females, with an incidence of 12 such tumors,

although an incidence of only 3.97 was to be expected.

The number of the remaining tumors (perineural fibroblastoma, tumors of the pituitary, teratoma, hemangioblastoma, cholesteatoma and ependymal cyst) was insufficient for division into separate groups. As a whole, the values for this group appeared to vary little from the expected value. Although the series is small, it is interesting to note that the neoplasms of the pituitary were equally distributed between the two races, the incidence for each being 6. The incidence of pinealoma for Negroes was 3, while that for the white patients was 1.

COMMENT

The material studied gives no indication of the reason that gliomas and meningiomas have a racial and sexual distribution. In Cushing's [2] series of meningiomas, only 7 occurred in members of the Negro race. He suggested that this low incidence was related to the protective influence of the Negro's thicker skull. It is difficult to believe that this factor could be operative to such a degree. As a matter of fact, the small degree of protection thus obtained could hardly compensate for the increased incidence of trauma to the head in Negroes. We believe that trauma has little, or nothing, to do with the development of these neoplasms. The fact that both gliomas and meningiomas are more frequent in females, the sex least exposed to head trauma, seems to bear out this belief. Cushing also reported that personal communications from Dr. C. C. Coleman, of Richmond, Va.; Dr. E. F. Fincher, of Atlanta, Ga.; Dr. Cobb Pilcher, of Nashville, Tenn., and Dr. G. S. Anderson, of New Orleans, revealed that these surgeons had seen only 5 instances of meningioma in Negroes. In recent communications from these men, Fincher reported having seen 3, and probably 4, cases of the tumor in Negroes, as compared with 44 cases among white persons. Pilcher had seen 3 cases of meningioma in Negroes and 20 in white persons. Coleman stated that he had seen a total of 9 cases of meningioma in Negroes.

With regard to the sexual incidence of meningiomas, 186 of Cushing's patients were females and 127 males. He expressed the belief that meningiomas were especially frequent among females when they occurred in certain regions of the body (spinal tumors, lateral tumors of the velum interpositum or pterional tumors *en plaque*). A similar sexual incidence was noted in his series of cases of neurinoma. Bradford,[3] in 1940, reported 4 instances of intraspinal meningioma in females, 3 of whom were Negroes. He cited Dr. S. R. Snodgrass, of Galveston, Texas, as having operated on a young Negro with another such tumor.

In Cushing's series of gliomas the reverse was true, males being affected more than females. Wilson,[4] in a summary of four series of gliomas (those of Tooth, Purves-Stewart, Dew, and Dowman and Smith), found 445 such tumors occurring in males and 316 in females. In the present series approximately the same sexual incidence of gliomas was noted, 49 occurring in males and 31 in females. When corrected, these values were approximately those to be expected; however, the incidence for white females, was definitely high, being 24 whereas the expected value was 11.38. Thus, in this series the frequency of gliomas in white females was nearly twice that in males. In contrast, the incidence for the Negro females was much lower than the expected value. Wilson also stated that glioblastoma multiforme was more common among males. This distribution was not noted in the present series. Bailey, Buchanan and Bucy [5] observed that medulloblastoma, also, was more frequent among males. The present series is too small to justify any conclusions in this regard.

The question arises as to whether the occurrence of these tumors in Negroes may be the result of dilution of the strain by cross breeding with members of the white race. The occurrence of gliomas in native African Negroes has been reported by Surmont and Sava [6a] and by van den Branden,[6b] but the racial purity in their cases was not established. In all probability, both gliomas and meningiomas occur in pure-blooded Negroes.

The fact that the life span tends to be shorter in the Negro race has been offered in explanation of the lower incidence of certain systemic tumors. In this series more autopsies were carried out on Negroes than on white persons in every age group except those beyond 60.

2. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938.

3. Bradford, F. K.: Spinal Meningiomas: A Report of Four Cases, Three of Which Were in Negroes, South. Surgeon **9**:722-732 (Oct.) 1940.

4. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, pp. 1186-1187.

5. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

6. (*a*) Surmont, J., and Sava: Tumors in Non-Civilized Negroes in Africa, Bull. Assoc. franç. p. l'étude du cancer **16**:136 (Feb.) 1927. (*b*) van den Branden, F.: Gliome du cerveau chez un nègre, Bull. Soc. path. exot. **13**:34, 1920; cited by Lewis, J. H.: The Biology of the Negro, Chicago, University of Chicago Press, 1942.

Since gliomas and meningiomas are most often seen in age groups below 60, the shorter life span could hardly be the explanation. Likewise, with respect to the distribution between the sexes, the males greatly exceeded the females in all age groups, including those beyond 60.

The low incidence of tumors among Negroes was not entirely restricted to tumors of the intracranial cavity. In the Negro patients in this series of autopsies there was a relatively low incidence of tumors of the biliary system (26 Negroes, 48 white persons), of the blood elements (45 Negroes, 71 white persons), of the respiratory system (68 Negroes, 100 white persons) and of the skin (32 Negroes, 54 white persons). In a total of 1,493 cases of malignant neoplasms encountered in this series of autopsies, there was a racial predilection for tumors arising either from mesothelial elements (sarcomas) or from epithelial elements (carcinomas).

CONCLUSIONS

Sex and race play an important role in the frequency of primary intracranial tumors.

The frequency of gliomas in white persons was approximately twice that in Negroes. This tumor was most frequent in white females.

Meningioma was approximately three times as frequent in white persons as in Negroes. Of the 28 meningiomas present, 12 occurred in white females.

The tumors which did not arise from either glial or meningeal elements showed no sexual or racial predilection.

USE OF FURMETHIDE IN TESTING SWEAT SECRETION IN MAN

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Sweating tests for the demonstration of various neural lesions received their impetus from the simple procedure introduced by Minor.[1] The use of drugs for the production of sweating has been limited chiefly to that of pilocarpine hydrochloride and mecholyl chloride (acetyl-betamethylcholine chloride). Sweating tests performed in this fashion have only a limited diagnostic value, being useful chiefly for demonstration of lesions of peripheral nerves (List and Peet[2]). However, in certain types of war casualties, lesions of peripheral nerves are common, and it has been my experience that the use of pilocarpine hydrochloride has not been wholly satisfactory as an agent to produce sweating. The usual dose of 10 to 12 mg. of the drug too frequently induces unpleasant side reactions, including urinary urgency, nausea and vomiting, in some patients, while others do not even sweat after this dose. When smaller doses have been employed, thirty to sixty minutes frequently passed before sweating occurred. In view of these experiences, it seemed desirable to seek some preparation which would induce sweating within a few minutes in most patients and would be relatively free from unpleasant side reactions. For this purpose a drug having a parasympathomimetic action, furmethide (furfuryltrimethylammonium iodide), was selected.

It has been demonstrated that furmethide is chiefly parasympathomimetic in its activity, although its chemical relation to acetylcholine is not direct. Furthermore, studies have indicated that furmethide is not an ester and that it is not related to the cholinesterase mechanism (Fellows and Livingston[3]; Myerson, Rinkel, Loman and Dameshek[4]). The first study on the effect of furmethide on various autonomic functions in man was presented by Myerson, Rinkel, Loman and Dameshek.[4] These investigators reported that after the parenteral injection of 3 to 5 mg. of furmethide the sweating reaction was pronounced, while the drug did not produce as conspicuous flushing and rhinorrhea as did mecholyl. Further, they reported that insignificant changes in blood pressure followed administration of furmethide to normal persons, while in some patients with hypertension the blood pressure was reduced to normal levels for a short time. Bondy and Altschule[5] investigated the effect of furmethide on the cardiovascular system in man, and the use of the drug for its detrusor action was studied by Lipton, Beaser and Altschule.[6]

METHOD

All tests were performed with the patient either sitting or standing at his bedside. Procedures such as forcing fluids, administration of acetylsalicylic acid or application of external heat were not employed. The iodine-starch technic of Minor was usually employed, and then either furmethide or pilocarpine hydrochloride was administered hypodermically into the deltoid region. Prior to the injection of either of these drugs the patient voided. When the examiner becomes sufficiently experienced, it is not necessary to employ the iodine-starch technic of Minor, as careful inspection and palpation will reveal the level of sweating if it is present.

Smith, Kline & French Laboratories, Philadelphia, supplied the furmethide.

From the Neurological Institute of New York, and the Department of Neurology, Columbia University College of Physicians and Surgeons.

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3. Fellows, E. J., and Livingston, A. E.: The Circulatory Action, After Atropine, of Certain Furfuryl Ammonium Iodides and of Acetyl-Beta-Methylcholine Chloride (Mecholyl), J. Pharmacol. & Exper. Therap. **71**:187-196, 1941; The Comparative Physiological Action of Analogous Trimethyl Ammonium Iodides of Benzene and Furane, ibid. **74**:65-70, 1942.

4. Myerson, A.; Rinkel, M.; Loman, J., and Dameshek, W.: The Effect of Furfuryl Trimethyl Ammonium Iodides on Various Autonomic Functions in Man, J. Pharmacol. & Exper. Therap. **68**:476-481, 1940.

5. Bondy, P. K., and Altschule, M. D.: The Action of Furmethide (Furfuryl-Trimethyl-Ammonium Iodide) on the Cardiovascular System in Man, Am. J. M. Sc. **204**:334-340, 1942.

6. Lipton, J. H.; Beaser, S. B., and Altschule, M. D.: The Action of Furmethide (Furfuryl-Trimethyl Ammonium Iodide) on the Bladder in Patients with Urinary Retention Following Surgery on the Rectum (Preliminary Report), New England J. Med. **226**:138-142, 1942. Beaser, S. H.; Lipton, J. H., and Altschule, M. D.: Further Experience with Furfuryl-Trimethyl-Ammonium Iodide (Furmethide) in the Treatment of Urinary Retention Due to Bladder Atony, Am. J. M. Sc. **206**:490-497, 1943.

OBSERVATIONS ON PATIENTS WITH NERVOUS DISEASES

A total of 35 adult patients received one or more doses of 5 mg. of furmethide in the deltoid region. Flushing of the face was noted within a minute, and usually within one to three minutes blue areas were present over the face; only 2 patients required as long as four minutes to show a sweating response in this region. Changes in color over the upper extremities, thorax and abdomen uniformly occurred in five minutes, except in 2 patients, who required six and eight minutes respectively for the appearance of these changes. Sialorrhea, rhinorrhea and lacrimation were not annoying concomitant reactions. Two patients had nausea and 5 urinary urgency. These symptoms were readily alleviated (within several minutes) by parenteral administration of atropine sulfate. In 1 patient, who had asthma, Raynaud's disease and scleroderma, rales and rhonchi developed; these were promptly relieved by the intravenous injection of atropine sulfate.

Ten of the patients who received furmethide were subsequently tested by parenteral administration of pilocarpine hydrochloride, in doses of 10 to 12 mg. Four patients did not exhibit any sweating response at the end of one hour, although 2 of them experienced urinary urgency and nausea. In 2 other patients the response was unsatisfactory after forty-five minutes. In the remaining 4 patients the response was satisfactory in from ten to twenty minutes, but 2 of these patients experienced nausea and urinary urgency. These side effects were not as readily abolished by atropine sulfate as those which appeared in the several subjects after the use of furmethide.

CONCLUSIONS

Furmethide manifested the following advantages over pilocarpine hydrochloride as a drug for testing the sweating response in man:

1. The sweating response of the face, upper extremities, thorax and abdomen usually appeared within two to five minutes after hypodermic injection into the deltoid region. Response to pilocarpine was slower, and in many instances there was no response.

2. Annoying side reactions following furmethide were rare and could be readily controlled with atropine sulfate. Side reactions following pilocarpine were more frequent, more annoying and less readily controlled by atropine sulfate.

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COLLOID CYST OF THE THIRD VENTRICLE

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Colloid cyst of the third ventricle is a relatively rare intracranial neoplasm. If recognized and treated surgically, it offers a favorable prognosis.[1] The clinical picture which such a tumor presents is not definite, but features of the history and physical signs suggest the correct diagnosis. However, the final diagnosis is dependent on the results of ventriculographic study.

Such a tumor rarely appears before the age of 20 years, and the distribution is about equal between the sexes. The duration of symptoms is variable. Dandy [2] stated that in about 50 per cent of all cases the signs and symptoms are of less than one year's duration. However, in Fuller's case symptoms were present for twenty years. The clinical picture in a typical case is one of severe intermittent headaches, which are bifrontal and may occasionally be relieved by a change in position of the head. Vomiting and nausea are usually associated with these headaches. Unilateral or bilateral motor and sensory symptoms and signs may appear; extraocular palsies, somnolence and mental changes are common. Periodic weakness of the legs is another frequent complaint. Zimmerman and German [3] stated that two important features of colloid cyst of the third ventricle are the almost uniform sudden onset of symptoms and the frequency of remissions. According to Stookey,[4] death frequently occurs during an attack.

It is thought that the attacks are due to acute obstruction of the foramen of Monro by the tumor's acting as a ball valve mechanism. Also, as the cyst becomes larger, it may cause signs and symptoms from pressure on tracts and nuclear masses adjacent to the wall of the third ventricle.[4] Stookey expressed the belief:

> Attacks may be due not only to obstruction of the lateral ventricles but also to compression of both veins of Galen at their origin, with coincident sudden interference with the venous outflow of the choroid plexuses of both lateral and third ventricles.

The neoplasm produces no accurate localizing signs and frequently causes false localizing signs, such as hemiplegia. The most common signs are atrophy of convolutions, noted in roentgenograms, papilledema, staggering gait, the Romberg sign, apathy, loss of memory, irritability, increased nervousness, carelessness, euphoria and disorientation.

This tumor is located in the anterosuperior portion of the third ventricle, and the ventriculographic picture is pathognomonic. Both lateral ventricles are symmetrically dilated and characteristically no air is shown in the third ventricle. The lateral ventricles may communicate with each other through openings in the septum pellucidum. Davidoff and Dyke [5] discussed in detail the ventriculographic and encephalographic pictures of these tumors.

The origin of the neoplasm is not certain, but most authorities now agree that it arises from the rudimentary paraphysis or the fetal ependyma. Zimmerman and German [3] expressed the belief that the cyst is usually derived from the choroid plexus of the third ventricle. "It also appears possible that rarely such a tumor may be derived from a persistent paraphysis." However, McLean,[6] after a thorough review of the embryology of this region, stated the belief that the colloid cyst arises from the paraphysis.

Jefferson and Jackson [7] characterized colloid cyst with the statement:

> It is inert, its secretion leads to no physiological derangement, it produces no localizing neurological signs, it lies as completely within the third ventricle as a tumor could

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7. Jefferson, G., and Jackson, H.: Tumors of the Lateral and Third Ventricles, Proc. Roy. Soc. Med. **32**:1105-1137 (July) 1937.

that was not free from all attachments, its effects are the result of cerebro-spinal fluid obstruction alone, its diagnosis is ventriculographic.

REPORT OF A CASE

History.—A married woman aged 49, white, entered the Massachusetts General Hospital in a comatose and incontinent condition.

The history obtained from her daughter revealed that she had been semicomatose during the week prior to admission. After an attack of phlebitis, in August 1942, she dragged her right foot when walking. During the month prior to admission she had severe intermittent

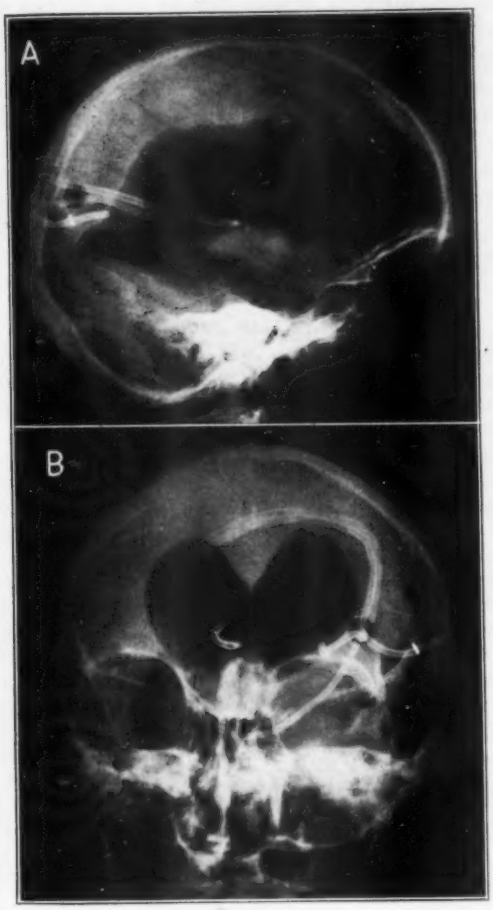

Fig. 1.—*A,* lateral view of the ventriculogram, showing the greatly enlarged lateral ventricles, and *B,* posteroanterior view, showing extreme dilatation of the lateral ventricles, with no displacement. The third ventricle is not visualized.

generalized headaches, and during these spells she vomited. She also exhibited a change in personality over the same period and made nonsensical remarks. The daughter added that her mother had not had any convulsions or fainting spells but that during the past year she had frequent attacks of falling, which apparently were due to both her legs[1] being weak and "giving out from under her."

The significant event in the past history was the removal of an ovary with "several little tumors" in January 1942. In August of the same year her right kidney was removed, but the reason for this could not be determined.

Examination and Course of Illness.—The patient was well developed. She was unresponsive, incontinent and extremely dehydrated. The pupils were small and reacted sluggishly, if at all, to light. The margins of the left optic disk were hazy; the right disk could not be well visualized, but its margins seemed to be hazy, too. The tendon reflexes were all normal and equal on the two sides. The Babinski response was elicited bilaterally. The blood pressure was 170 systolic and 110 diastolic.

The results of laboratory studies were all within normal range. Roentgenograms of the skull and chest showed nothing abnormal. An occipital ventriculogram, made on the following day, revealed extreme symmetric dilatation of the lateral ventricles, with no displacement. The third ventricle was not visualized. Rubber catheters were placed in the lateral ventricles and sutured to the skin.

The day following the ventriculographic examination the patient became responsive and appeared much better, even though she remained incontinent and was disoriented. Indigo carmine was introduced into the right

Fig. 2.—Section of the brain, showing a portion of the tumor protruding through the foramen of Monro into the right lateral ventricle.

ventricle, and the catheters were removed. It was decided then to make a pneumoencephalographic examination and to attempt to outline the third and fourth ventricles, as well as to determine whether there was a complete block in the third ventricle.

The following day her temperature began to rise, and stiffness of the neck developed. She was given sulfadiazine, but in spite of this medication and ventricular taps she died.

Pathologic Study.—Examination of the brain showed pronounced hydrocephalus of the lateral ventricles, with a neoplasm in the anterior portion of the third ventricle. This growth was attached to the roof of the third ventricle, and a portion of it protruded through the foramen of Monro into the right lateral ventricle. The tumor was composed of a thin capsule surrounding a mass of gray, gelatinous colloid material.

The wall of the cyst was lined by a single, uniform layer of nonciliated cuboidal cells with large round or ovoid nuclei, dusted with fine chromatin granules. The cytoplasm was finely granular and often vacuolated, and the cell boundaries were ill defined. There was no obvious basement membrane, and the epithelium lay

on a thin layer of wavy, relatively acellular, collagenous tissue, which contained a few capillaries and one or two small blood vessels. Sections of the contents of the cyst revealed a structureless, homogeneous, eosinophilic material, closely resembling colloid of the thyroid, with groups of large and small monocytes.

The histologic character of this tumor was essentially the same as that of the other colloid cysts which have been reported. Some of the other cysts were lined by more than one layer of cells, and in some cases the epithelial cells were ciliated. The colloid material stained pink with hematoxylin and eosin, and monocytes were usually present.

In retrospect, the history and physical signs, together with the ventriculographic evidence, were characteristic of a colloid cyst of the third ventricle. The patient had had severe intermittent headaches associated with vomiting, changes in personality and transitory attacks of weakness of both legs. Physical examination revealed nothing of significance except for the stupor, the blurred margins of the disks, contraction of the pupils, which reacted only sluggishly to light, and a bilateral Babinski response. The ventriculograms showed pronounced dilatation, without displacement, of the lateral ventricles and absence of air in the third ventricle.

Massachusetts General Hospital.

Clinical, Technical and Occasional Notes

VISIBLE RETINAL ARTERIOLAR SPASM ASSOCIATED WITH MULTIPLE SCLEROSIS

Preliminary Report

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In this note is reported a phenomenon associated with multiple sclerosis which, so far as we know, has not previously been described. Associated with abrupt attacks of visual impairment consisting of shimmering and the presence of multiple dark areas, spasm of the retinal arterioles could be seen on examination with a Morton ophthalmoscope. In the first case brief inhalation of amyl nitrite abolished both the spasm and the visual impairment. In the second case the same phenomenon occurred, except that the attacks disappeared spontaneously. In the third case attacks of blurred vision were relieved by amyl nitrite.

REPORT OF CASES

CASE 1.—F. M., a white woman aged 30, had a neurologic ailment which had been diagnosed as multiple sclerosis by several observers. She was referred to one of us by Dr. Bernard Glueck. In May 1943 she began to stagger to the right side for brief periods, the attacks coming and going. At the same time vision was impaired. Tingling and numbness of both hands began in July 1943; at first the paresthesia came and went, but it had been continuous since October. Weakness and turning of both ankles, as well as tingling on the left side of the abdomen and numbness of both lower extremities, began in November 1943, and there had been occasional diplopia since November. Examination on Feb. 4, 1944 disclosed a somewhat unsteady gait, with a moderately wide base, and impairment of succession movements in both hands. The deep reflexes were all greatly increased; the abdominal reflexes were absent, and there was a Babinski sign on the right side. Position sense was questionably impaired in the big toes. The muscles of the right side of the face were weak. The right optic disk showed definite, and the left questionable, temporal pallor.

The patient also had permanent visual impairment, as evidenced by the presence of several small scotomas on every examination of the visual fields.

She stated that her visual symptoms were always worse after a warm bath. Examination of the visual fields immediately after such a bath regularly showed an increase in the number of scotomas. In addition, examination of the fundus immediately after a warm bath during periods of increased visual disturbance regularly showed spasm of the retinal arterioles. In one examination the whole arteriolar tree of the right retina was obliterated. At other times, only single vessels seemed to be involved; usually the appearance was that of beading of a vessel, although once an entire arteriole continued to open and close as a whole. Spasm and increased visual impairment were always concomitant.

Brief inhalation of amyl nitrite always produced immediate abolition of both spasm and symptoms. It can be said that brief clinical attacks of one of the phenomena of multiple sclerosis were produced and relieved within a few minutes by this procedure.

Further investigation revealed that the visual attacks were also elicited by the heat of a hair drier and, to a mild degree, by a hot drink or the taking of hot, spicy food.

CASE 2.—R. A., a white man aged 38, had a disturbance which had been diagnosed as multiple sclerosis by several observers. He was referred by Dr. David Beck. Intermittent impairment of vision began in the spring of 1934; it soon became constant and then, in the course of two months, disappeared. In the spring of 1935 numbness of the right hand and the right side of the face appeared, accompanied by slurring of speech and dragging of the right leg. Complete recovery occurred in a few weeks, after administration of fever treatment at the Mount Sinai Hospital. Easy fatigability had been present since the summer of 1940. Transient visual impairment had occurred about once a week since the onset. Neurologic examination on Nov. 15, 1940, and at intervals since, revealed only the absence of all abdominal reflexes, except that in the left upper quadrant, which, however, was feeble, and slight but definite bitemporal pallor.

R. A. also had a permanent scotoma in each eye. A hot drink increased his visual disability subjectively and the size of the scotomas on examination of the visual field. Spasm was observed ophthalmoscopically in the arterioles of the macular region after the taking of a hot drink, in association with the increase in the size of the scotoma. The attacks were too brief for relief by amyl nitrite, and since they did not occur after every hot drink, their attempted prevention by amyl nitrite has not yet seemed feasible.

CASE 3.—A. P., a white woman aged 30, had a disturbance diagnosed as multiple sclerosis by several observers. The illness began in March 1939 with nausea, vomiting, vertigo on her turning the head to the left, staggering and double vision. The symptoms became reduced in intensity, but staggering, diplopia and mild vertigo continued to recur. In May 1942 there was a severe recurrence of all symptoms, and intention tremor and numbness in the thigh and in all the fingers on both sides appeared for the first time. Since then, all the symptoms have recurred and disappeared frequently, and easy fatigability has been prominent. Examination at the Mount Sinai Hospital in May 1942 showed a broad-based gait; ataxia of both upper extremities; ataxia of the left lower extrem-

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ity; exaggeration of all deep reflexes, those on the right being more active than those on the left; greatly diminished abdominal reflexes; paresis of the right external rectus muscle, and bitemporal pallor. At other times the patient showed a Babinski reaction on the right side and paresis of the left inferior rectus and the right superior and internal rectus muscles. The results of examination at the time of writing were essentially the same as in May 1942.

A. P. had frequent morning attacks of diplopia or of blurred vision. Inhalation of amyl nitrite cleared up these attacks immediately, and they did not return until the next morning.

Abrupt attacks involving various parts of the central nervous system, including the visual apparatus, are common in cases of multiple sclerosis. Usually they last more than a few minutes or a few hours. However, sudden attacks of one kind or another of brief duration are also not uncommon in the disease. Arteriolar spasm associated with such attacks and relief of symptoms with amyl nitrite form the subject of this report.

SUMMARY

In 2 cases of multiple sclerosis, spasm of the retinal arterioles was coincident with the presence of scotomas. When the scotomas receded or disappeared, the spasm also disappeared; this change followed immediately the inhalation of amyl nitrite in one case and was spontaneous in the other. In a third case attacks of blurred vision were promptly relieved by inhalation of amyl nitrite.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

DEGENERATION AND REPAIR OF THE RAT RETINA IN AVITAMINOSIS A. MYRA L. JOHNSON, Arch. Ophth. **29**:793 (May) 1943.

Although night blindness and various ocular disturbances have for centuries been associated with dietary deficiency, it is only within recent years that vitamin A deficiency has been identified as the specific cause of these defects. Clinical observations suggest that the condition is purely a functional disorder, due to the simple lack of a substance essential to the visual processes, and hence a disorder which might be cured by supplying adequate amounts of the missing vitamin A. Many observers have noted that normal visual acuity is not immediately restored when an adequate amount of vitamin A is added to the diet. In instances in which the condition responds slowly, if at all, to continued vitamin A therapy, something more which is essential to the formation of visual purple seems to be lacking.

Johnson found that the retinas of rats with acute severe avitaminosis A of short duration showed no structural changes other than general edema. When the avitaminosis continued over a long period (at least ninety days, or until the rats were apparently moribund) degeneration appeared in the visual cells in the outer nuclear layer, the inner nuclear layer, the outer molecular layer and the layer of pigmented epithelium. Lesions which involved the greater part of the outer nuclear layer were irreparable after ten to eighteen weeks of recovery therapy.

A remarkable degree of repair after twenty-four hours of vitamin therapy was shown in the outer segments of rods which had undergone only slight degenerative changes as a result of avitaminosis A, and there was a practically complete return to the normal condition after twenty-one to twenty-eight days of recovery. It was demonstrated that the outer segments of rods, and possibly the inner segments as well, which had completely degenerated as a result of vitamin A deficiency were incapable of regeneration in rats that were adequately fed for a period of ten to eighteen weeks after the deficiency.

SPAETH, Philadelphia.

STRUCTURAL CHANGES IN EXTERNAL GENICULATE BODY OF RAT FOLLOWING REMOVAL OF EYES. ROBERT R. CHACE, Arch. Ophth. **30**:75 (July) 1943.

Chace removed both eyes at birth in 19 rats. Beginning two weeks after operation, and thereafter at frequent intervals, up to one year, he killed the animals and made gross studies of the brain, including a comparison with normal control animals. In addition to these 19 rats, 2 others were studied which were born, to all appearances, without eyes. In the brains of rats born with microphthalmos or with degenerated eyes there were absence of the optic chiasm and tracts and hypoplasia of the external geniculate bodies. The removal of one eye from a newborn rat resulted in hypoplasia of the external geniculate body on that side, with degeneration of the optic nerve and tract corresponding to the enucleated eye. Removal of one eye in an adult animal was followed by atrophy of the optic nerve, but there were no changes in the chiasm or in the external geniculate body.

SPAETH, Philadelphia.

A NEW ANSWER TO THE QUESTION OF MACULAR SPARING. F. H. VERHOEFF, Arch. Ophth. **30**:421 (Oct.) 1943.

According to ordinary field tests, the central visual field is usually spared to a considerable extent when one occipital lobe has been removed or its functions have been completely destroyed, while the central field is characteristically split vertically when one optic tract is destroyed. If there is actual sparing of the macula in the former case, there seems to be no escape from the conclusion that bilateral representation of the macula exists in the occipital lobes. There is, however, no tenable anatomic evidence in favor of this, and, in fact, much against it. Assumption that the supposed sparing is due to instability of fixation fails to solve the enigma because it does not explain why such sparing is not found when one optic tract is destroyed. The theory that Verhoeff offers explains macular sparing after complete destruction of one occipital lobe as only apparent and as due partly to instability of fixation and partly to the establishment of an eccentric fixation point. It also accounts for the instability of fixation after lobar destruction and for absence of apparent sparing after complete destruction of one occipital lobe. In addition, his theory accounts for the instability of fixation after lobar destruction and for absence of apparent sparing after interruption of one optic tract. The theory, in brief, is that apparent sparing results from loss of necessary cortical integration and that this loss may be produced by cortical injury, but not by unilateral representation of the macula, and is based on the following considerations:

If one looks at a circle on a uniform white background and the circle corresponds in size to the macula, one can accurately fixate the center whether or not an actual point is there. If half the circle is hidden by a large piece of black paper with a straight edge that passes vertically over the center of the circle, one can still precisely fixate the center with the fovea. Evidently, therefore, if the cerebral cortex is intact, the integration and correlation in question can take place when there is no retinal image on one half of the macula. However, since one completes the circle by the imagination, it can be said that there is an imaginary image on one half of the macula. Obviously, when one optic tract is interrupted an analogous condition exists—one half of the visual field is blocked off while the cerebral cortex remains intact. Hence fixation is normal and splitting of the macular field can be found. This would be the case also if corresponding halves of the retinas were destroyed. When, however, one occipital lobe has been destroyed or removed, and the integration in question is thereby abolished, fixation becomes eccentric and apparent sparing is found. It would seem that the new retinal point of fixation would be at about the center of the remaining macula. This would account for apparent sparing of about three fourths of the whole macula.

The remainder of the apparent sparing could be accounted for by fixation slippage dependent largely on the altered correlation with the oculomotor mechanism.

The author then calls attention to the fact that while certain lesions and operations, such as the removal of the right hemisphere, contradict bilateral representation of the macula in the occipital lobes, they also seem to contradict his theory as just presented. With this in mind, Verhoeff elaborates his theory in detail. It is sufficient to say at this time that apparent sparing of the macula after complete destruction of one occipital lobe may be explained by loss of integration between the seeing eye and the blind field in the conscious visual cortical area in use. As a result of this loss an eccentric retinal point is employed for fixation, and slippage in fixation occurs. The original macular field is exactly split through the center but in field tests appears to be more or less spared. When one optic tract is interrupted, the integration in question is not disturbed, and splitting of the macula is therefore found in field tests. Even after complete destruction or removal of one occipital lobe, macular splitting may be found in such tests if integration in the conscious visual area in use is not too greatly disturbed. These conditions would most likely obtain when the lobe destroyed was on the side opposite that of the conscious visual area.

Verhoeff states that his theory needs additional facts before it can be unreservedly accepted. Nevertheless, it seems sufficiently satisfactory to warrant the statement that the field determinations thus far made do not refute the evidence against bilateral occipital representation of the macula. SPAETH, Philadelphia.

EFFECTS OF MORPHINE IN EXPERIMENTAL SHOCK DUE TO HEMORRHAGE. A. BLALOCK, Arch. Surg. **47**:326 (Oct.) 1943.

Blalock studied experimentally the effect of morphine in conditions of severe hemorrhagic shock. In 20 dogs shock was produced by bleeding; 10 of the animals received morphine; the other 10 served as controls. In both groups the animals died when approximately half the total blood volume was lost. The chances of survival were apparently not lessened even by administration of large doses of morphine. In human patients, however, morphine may possibly impair the chances of recovery by causing nausea and inadequate oral intake of fluids. LIST, Ann Arbor, Mich.

Psychiatry and Psychopathology

MANIC-DEPRESSIVE PSYCHOSES AMONG COLLEGE STUDENTS. LEONARD E. HIMLER and THEOPHILE RAPHAEL, Am. J. Psychiat. **99**:188 (Sept.) 1942.

Himler and Raphael encountered 79 cases of manic-depressive psychosis in eleven years among students at the University of Michigan. Seven and six-tenths per cent of the students required the attention of the mental health unit, and in less than 1 per cent of this number did manic-depressive psychoses develop. The incidence was higher among women students. A majority of the patients were referred by the student health physicians, and 78.5 per cent had their first attack while in college. Because of early recognition and therapy of the disease, 60 per cent of the students were able to complete the term in which the episode occurred, and all but 28 per cent were able to continue their college work. More than a third of the patients continued their academic work without interruption. FORSTER, Boston.

BILATERAL PREFRONTAL LOBOTOMY. LLOYD H. ZEIGLER, Am. J. Psychiat. **100**:178 (Sept.) 1943.

Zeigler gathered statistics on the results of prefrontal lobotomy from eighteen centers in the United States and Canada. Of the 618 cases collected, those of schizophrenia, depressions, especially the involutional type, and obsessive neurosis predominated. The ages ranged up to 70 years. Twelve patients died as a result of the operation; 18 died subsequent to the operation; the condition of 70 patients was not improved or was rendered worse; that of 303 patients was improved to some degree, and 215 patients recovered from their psychotic or neurotic symptoms. Zeigler concludes that this operative therapy deserves a fair trial for the next five or ten years. FORSTER, Philadelphia.

ENVIRONMENTAL AND PERSONALITY FACTORS IN THE PSYCHOSES. IRENE CASE SHERMAN and SAMUEL H. KRAINES, J. Nerv. & Ment. Dis. **97**:676 (June) 1943.

Sherman and Kraines evaluate the information contained in the hospital records of mentally sick patients. They used data sheets on which a large number of items (769) were tabulated. The records of 97 patients with schizophrenia and 43 patients with manic-depressive psychoses were studied with the object of analyzing the personality and behavior characteristics of the two groups.

In both groups, "only" children were infrequent, and siblings other than the oldest or the youngest were more common than either of the extremes. The schizophrenic patients were more likely to be the product of a broken or disharmonious home. Likewise, dominating and conceding parents were more frequent among these patients. On the other hand, the presence of an unstable parent was more common in the homes of patients with manic-depressive psychoses.

Poor social energy was striking in the schizophrenic patients. Persons who become schizophrenic seem to have an organic deficiency which limits their ability to deal with their environment. They have a "weak battery." The schizophrenic patients were described as shy, shut in, jealous, hypersensitive and narrow, while the patients with manic-depressive psychoses were superior in three characteristics; that is, they were well adjusted, outgoing and prudent.

Physical illnesses and weakness before puberty were much more common in schizophrenic patients, while after puberty severe illnesses or operations were twice as frequent among patients with manic-depressive psychoses. After puberty, schizophrenic patients had more difficulty in getting along with others and had more financial troubles and sexual conflicts.

The early changes in personality and behavior preceding the acute breakdown in schizophrenic patients were in the direction of greater seclusiveness and sensitivity, complaints of bodily pain, odd behavior and greater quietness and shyness. The early changes presented by the patients with manic-depressive psychoses were increased restlessness, overactivity, decline in work, insomnia, moodiness, fatigue and worry.

During the acute period preceding commitment, the manic-depressive patients displayed greater tension, excitement and instability, while the schizophrenic patients were untidy and suspicious and showed poor judgment.

In the ward the patients with manic-depressive psychoses were overactive and excited, while the schizophrenic patients showed compulsive behavior, mannerisms, seclusiveness, stereotypy and negativism. The dominant affect of the patients with manic-depressive psychoses was depression and unmotivated crying,

while that of the schizophrenic patients was apathy and unmotivated laughing. The schizophrenic patients were, surprisingly, more labile than the patients with manic-depressive psychoses. In the two groups speech was retarded with equal frequency, but that of the schizophrenic patients showed characteristic irrelevance. Bizarre ideas, auditory hallucinations and delusions of persecution were characteristic of the schizophrenic patients, while ideas of reference and somatic delusions appeared with equal frequency in the two groups.

The symptoms most common in the schizophrenic patients were delusions of persecution; irrelevant speech; seclusive, manneristic, untidy and uncooperative behavior, and emotional indifference. Both psychoses differ from other illnesses in that they are characterized by disorganization of personality and lack of behavioral integration. In schizophrenia the disturbance is in the higher symbolic levels which regulate social behavior. In manic-depressive psychoses lower levels which ordinarily maintain physiologic equilibrium are primarily involved. CHODOFF, Langley Field, Va.

PSYCHIATRIC INDUCTION EXAMINATIONS. DAVID J. FLICKER, War Med. **2**:931 (Nov.) 1942.

Flicker reviews the literature on the neuropsychiatric examinations of selectees and reports a study of the work of the induction board at Camp Blanding, Fla., from Dec. 1, 1940 to Nov. 1, 1941. In this period 16,882 men were examined. Of these, 3,059 were rejected for all causes; 283 were rejected for neuropsychiatric reasons only, and 42, for neuropsychiatric and other reasons. The screening neuropsychiatric examination took two to three minutes, all men presenting difficulty in diagnosis being rechecked, the recheck taking about fifteen minutes.

As a result of this study the author makes the following recommendations: 1. Local boards should furnish the psychiatrist with a psychiatric history of each selectee. This could be obtained by a social worker. 2. The psychiatrist should be allowed more time per examination. 3. More trained psychiatrists should be used in making examinations. 4. The psychiatrist should not be asked to examine more than 50 selectees a day and should be able to spend at least five minutes with each man. 5. There should be a special neuropsychiatric blank, like the one used at Camp Blanding. 6. There should be a period of psychiatric observation before the selectee is finally inducted. PEARSON, Philadelphia.

Diseases of the Brain

INTRACRANIAL ANEURYSMS. MAX H. WEINBERG, J. Nerv. & Ment. Dis. **97**:666 (June) 1943.

Weinberg reports 3 cases of intracranial aneurysm, with special emphasis on their individual symptoms. The first case was that of a boy aged 12 years who suddenly became faint while playing and quickly exhibited signs of meningeal irritation, with bloody spinal fluid. During apparent recovery, he relapsed, had a convulsive seizure and died. Autopsy revealed a necrotic cavity, containing blood, in the left frontal lobe. An insignificant branch of the left anterior communicating artery was apparently the site of the aneurysm. In the second case, headache which had been present for years cleared up entirely after the patient recovered from the effects of the rupture of an aneurysm. The third case was that of a man aged 67 with complaints of headache and increasing lethargy. A roentgenogram of the skull revealed calcification in the walls of the internal carotid artery with some aneurysmal dilatation, and it was thought that this was responsible for the symptoms. CHODOFF, Langley Field, Va.

HEMIATROPHY OF BRAIN WITH CONTRALATERAL CEREBELLAR ATROPHY. JACK MOORE, J. Nerv. & Ment. Dis. **98**:31 (July) 1943.

Hemiatrophy of the brain, a rare condition, occurs either as a pure cerebral lesion or with associated atrophy of the opposite side of the cerebellum due to concomitant involvement of the basal ganglia. The pathogenesis is variable—vascular, inflammatory and congenital causes having been ascribed to cases described in the literature. Moore reports the case of a middle-aged patient who began to have convulsive seizures at the age of 13 years, followed by signs of left hemiplegia with contractures and the gradual development of a paranoid type of psychosis. He died after a generalized convulsion, and autopsy revealed atrophy of the entire right cerebral hemisphere and the basal ganglia on the same side, as well as of the opposite cerebellar hemisphere. The absence of cerebellar and extrapyramidal symptoms is explained by the early loss of function of the pyramidal tract, which masked the symptoms of cerebellar tonic and coordinating dysfunction. The case is included under the secondary, or acquired, rather than the congenital, form of hemiatrophy of the brain. CHODOFF, Langley Field, Va.

OBSERVATIONS IN ELECTRIC SHOCK THERAPY APPLIED TO PROBLEMS OF EPILEPSY. LOTHAR B. KALINOWSKY and FOSTER KENNEDY, J. Nerv. & Ment. Dis. **98**:56 (July) 1943.

Application of electric shock therapy to a large number of patients permitted various observations with respect to convulsions and the epilepsies in general. Certain differences between the convulsions produced by metrazol and those produced by electric shock were noted, with respect to both the actual seizure and the postepileptic phenomena.

For electric shock men tended to have lower thresholds than women. A reduction in threshold of 20 to 30 volts could be produced by the use of the McQuarrie pitressin-water test. Various drugs were used as sedatives, and it was found that bromides showed no anticonvulsant activity, whereas diphenylhydantoin sodium produced a dramatic rise in the convulsive threshold. Barbiturates (barbital sodium and phenobarbital) had a moderate anticonvulsant effect.

After seizures had occurred, there was a spontaneous rise in threshold for subsequent treatments. In a series of 12 patients with epilepsy to whom electric shocks were given, it was found that the convulsive threshold was raised by artificial induction of fits to the same extent as that for nonepileptic patients. It was also found that the convulsive threshold of epileptic patients was no lower than that of nonepileptic patients. Thus, electric shock is of no value as a diagnostic aid in epilepsy. However, the spontaneous rise in threshold which is produced by a convulsion may be used to break up psychic equivalents, which might be long lasting if not terminated by an artificially produced seizure. CHODOFF, Langley Field, Va.

ELECTROENCEPHALOGRAPHIC STUDY OF TWO HUNDRED AND SEVENTY-FIVE CANDIDATES FOR MILITARY SERVICE. JOHN E. HARTY, ERNA L. GIBBS and FREDERIC A. GIBBS, War Med. **2**:923 (Nov.) 1942.

The authors found that 30 per cent of 275 candidates for military service had abnormal electroencephalo-

grams, as compared with only 15 per cent of a superior control group—medical students, hospital staff, etc. Of the 275 men, 127 had a history of severe head injury or of neuropsychiatric disorders.

If these 127 men are excluded, the proportion of candidates with abnormal electroencephalogram is only 13 per cent. Epileptoid types of electroencephalographic abnormality were five times as common for men with a positive history as for men without. For practical purposes the electroencephalogram must be evaluated with the history. It is useful in focusing suspicion on certain persons, who can then be given a more thorough neuropsychiatric examination, and is valuable for persons for whom the results of other tests are equivocal or borderline.

PEARSON, Philadelphia.

TORULOSIS OF THE CENTRAL NERVOUS SYSTEM. DONALD BLAIR, J. Ment. Sc. **89**:42 (Jan.) 1943.

Blair describes the third case of torulosis of the nervous system to be reported in Great Britain. A man aged 45 had been ill for ten weeks before his admission to the department of psychiatry of a general hospital. The onset of the illness was characterized by severe frontal headache, fever, general malaise and slight muchal rigidity, all of which cleared up in one month. The patient was discharged, but headache returned within a few days, this time accompanied by pronounced meningeal signs. A month later the earliest psychotic symptoms appeared, consisting chiefly of quantitative mental loss, paranoid trends and agitation. He died shortly thereafter.

Autopsy revealed congestion of the blood vessels of the brain and a diffuse, yellow-brown, gelatinous material in the subarachnoid space over each hemisphere, as well as in the ventricles. No cysts were observed. A histologic study of sections of the brain was not made. Embolic colonies of torulas were noted in the kidneys, as well as in the lungs.

PEARSON, Philadelphia.

Treatment, Neurosurgery

CONGENITAL PARALYSIS OF LATERAL ROTATORS OF EYES WITH PARALYSIS OF MUSCLES OF FACE. AVERY M. HICKS, Arch. Ophth. **30**:38 (July) 1943.

Congenital bilateral paralysis of the muscles which move the eyes in the horizontal plane and congenital bilateral paralysis of the muscles of the face occasionally occur together. This disabling congenital anomaly makes up a small group of congenital defects which probably form a step in the transition between certain forms of congenital absence of abduction and the congenital ophthalmoplegias. Various authors have described this condition from time to time, with an occasional pathologic report showing hypoplasia of the brain stem in the area of the sixth and seventh cranial nerves.

This combination of paraylsis of the lateral rotators and both abductors and adductors with normal vertical movements of the eyeballs but with disturbances in the function of the muscles of face is frequently spoken of as the Möbius syndrome. It was first described by him in 1888 and, later, in 1892.

Hicks reports 4 cases of this syndrome and reviews the theories responsible for the condition.

The exact nature and site of the lesions which produce the Möbius syndrome are not known. It is probable that the site, nature and extent of the lesion are different in various cases. In cases in which nystagmus is absent on vestibular stimulation and there is a response of the internal rectus muscle to impulses of convergence but not to impulses for associated movements, as in case 3 of the author's series, the lesion probably interferes with the continuity of the fibers of the posterior longitudinal fasciculus, so as to prevent the impulses originating in the vestibular apparatus from reaching the nucleus of the third nerve. This nucleus and the fibers to the internal rectus muscle must be intact; otherwise, convergence would be impossible. The lesion is probably at the level of the nuclei of the sixth and seventh cranial nerves, but may extend above and below the level of these centers. In case 4, that of a boy with poor convergence and weakness of the upward and downward rotations, the disease process had probably extended upward to involve a portion of the nucleus of the third nerve.

Several theories have been advanced to account for the nature of the disease process which produces this clinical picture. The best known are Möbius' theory of intrauterine nuclear disease, Kann's theory of congenital aplasia of part of the brain stem and Hübner's theory of hypoplasia of the brain stem. Hübner based his theory of hypoplasia on the anatomic examination of the brain stem of a 19 month old boy who showed complete bilateral absence of abduction with paralysis of the muscles of the face. The involvement of the facial musculature was more pronounced on the left side, and there was atrophy of the left half of the tongue. Postmortem examination disclosed marked defects in the motor ganglia and nerve fibers in the medulla and the pons. There were practically no cells in the nuclei of the facial, hypoglossal and abducens nerves. There were no signs of degeneration or inflammation, and Hübner concluded, therefore, that the defect was due to hypoplasia. The clinical phenomena offer no basis on which to judge the value of the various theories; in fact, it is not possible to determine whether the anatomic anomalies observed in the muscles represent primary or secondary changes. Thus, one must conclude that this congenital anomaly is due to a pathologic process of an unknown nature involving the brain stem.

SPAETH, Philadelphia.

AN OPERATION FOR SCAPHOCEPHALY. W. E. DANDY, Arch. Surg. **47**:247 (Sept.) 1943.

Dandy describes a new operative procedure for the relief of scaphocephaly. A large frontoparietal bone flap is turned. The mesial border of this flap serves as a hinge, the lateral free border being elevated about 3 cm. and fixed by a free bone graft. The dura is opened under the flap for decompression. The operation must be performed on both sides, with an appropriate interval between the two stages. It is advisable to operate when the patient is very young, for the procedure is then technically easier and signs of cerebral compression have not yet fully developed. The cosmetic result obtained appears to be excellent.

LIST, Ann Arbor, Mich.

PREFRONTAL LOBOTOMY IN THE TREATMENT OF MENTAL DISEASES. M. C. PETERSEN and F. P. MOERSCH, Proc. Staff Meet., Mayo Clin. **18**:368 (Oct. 6) 1943.

Moersch reports that prefrontal lobotomy has been performed on 42 patients who had been ill with mental disease for a long time and who had received little or no help from other treatment. As a result of experience with these patients, he states that the operation did

most for patients with depression but not much for schizophrenic patients. In well selected cases the procedure is justifiable, although it is not a panacea.

Petersen cites Penfield and Evans as describing patients who had had a unilateral lobectomy as good natured, cooperative and easy to get along with. He mentions Jacobsen's chimpanzee which was conditioned by too difficult tests to neurotic responses. Bilateral lobectomy resulted in cheerful, though more inefficient, performance of the tests. These observations on lobectomy led to the first lobotomy by Moniz and Lima, of Portugal, in 1935.

Petersen describes the results he has seen as follows: relief from worry and anxiety, untidiness (due to lack of attention rather than to lack of control), persisting for several weeks after operation, and pronounced flushing and sweating shortly after the ablation in most cases. The vasomotor disturbance was accompanied by slowing of the pulse (often permanent); the cold extremities became warm; the blood pressure dropped, returning to the initial level in several weeks or months, and the appetite, and in some cases the weight, increased. Changes in the sugar tolerance curves and in gastric acidity after operation are cited as indicative of the importance of hypothalamic function in these cases.

Four cases are reported: case 1, that of a depressed elderly woman, who was to undergo lobotomy; case 2, that of a depressed woman who was relieved from anxiety and worry by operation and showed no untidiness and only slight confusion about a month later; case 3, that of an elderly agitated and depressed woman with postoperative relief from anxiety and worry and no untidiness, but with some increase in confusion in the second week after operation, and case 4, that of an elderly woman with similar relief from worry and "no untidiness and practically no confusion."

McCarter, Philadelphia.

PREFRONTAL LOBOTOMY IN THE TREATMENT OF MENTAL DISEASE: SURGICAL TECHNIQUE. J. G. LOVE, Proc. Staff Meet., Mayo Clin. **18**:372 (Oct. 6) 1943.

In this operation, Love uses only three special instruments, in addition to a dissection set: a trephine, a Killian nasal septum elevator, as a cutting instrument, and an Adson speculum.

The procedure is that of Dr. J. B. Lyerly, of Jacksonville, Fla. At a point 3 cm. anterior to a line drawn over the vault from the external auditory meatuses and 3 cm. on each side of the sagittal suture trephine openings are made. "The two layers of the dura mater are reflected in opposite directions to facilitate closure of the wound." After an avascular portion of the pia arachnoid is incised, the Killian nasal septum elevator is introduced into the frontal lobe.

At first the intrument was swung around below the cortex in an arc to cut all association fibers, but since it was suggested that this was producing too much "masking," a modification which Love and Uihlein call a "grade 3 operation" is employed. This involves "swinging across a line which is parallel to the floor of the anterior cranial fossa" and comes up slightly laterally, and also mesially. In Petersen's cases this modification was used. A grade 2 operation (hypothetic as yet) would be "an incision across the floor of the anterior fossa," and a grade 1 operation, just "a slit down the center of the white matter."

In a series of 42 cases there were no deaths, and in only 1 case were there postoperative convulsions.

McCarter, Philadelphia.

News and Comment

APPOINTMENT OF CHIEF OF DIVISION OF NEUROPSYCHIATRY, MONTEFIORE HOSPITAL

The board of trustees of Montefiore Hospital for Chronic Diseases announce the appointment of Dr. H. Houston Merritt, associate professor of neurology at Harvard Medical School and visiting neurologist at the Boston City Hospital, to the position of chief of the division of neuropsychiatry of Montefiore Hospital, to take effect September 1.

Dr. Merritt will be in full time charge of the investigative and clinical work of the division of neuropsychiatry of Montefiore Hospital and professor of clinical neurology at Columbia University College of Physicians and Surgeons in charge of the teaching at Montefiore Hospital.

Dr. Merritt will succeed Dr. S. Philip Goodhart, who is retiring from his position after thirty-one years of service at Montefiore Hospital and who has been awarded the rank of consultant on the division of neuropsychiatry.

AMERICAN BRANCH OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY

At the annual meeting of the American Branch of the International League against Epilepsy, held in Philadelphia on May 14, the following officers were elected for the ensuing year: president, Dr. Charles D. Aring, Cincinnati; vice president, Dr. Haddow M. Keith, Rochester, Minn., and secretary-treasurer, Dr. Frederic A. Gibbs, Boston.

Society Transactions

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

HENRY A. LUCE, M.D., *President, in the Chair*

Regular Meeting, Oct. 23, 1943

Individual Issues in Postmilitary Psychotherapy. DR. JOHN C. WHITEHORN, Baltimore (by invitation).

In the ardent search for generalizations about wartime psychiatric conditions, there is danger of getting into systematic error, through neglect of individual issues. It is quite natural, and wise, to seek for common denominators. In the military service there is great difficulty in individualizing case study and treatment. We civilians have at times opportunities for studying and evaluating some of the more distinctively personal trends which have contributed to shaping the issues encountered, disastrously, in the military service. These are not all included, by any means, under fear of combat or of physical injury.

Case studies of ex-soldiers were briefly presented. One man, for example, had shown a reaction which might be called a promotion panic, with intense preoccupation with officer responsibility. Another, an officer candidate, had worked himself into a dense fog of confusion in attempting an anticipation to evaluate his qualities of leadership. These cases were utilized to point out the general principle that the stress and meaning of a particularly military situation depend in considerable measure on the personality problems of the individual soldier and the issues about which he, as an individual, is prepared to develop anxiety.

HENRY A. LUCE, M.D., *President, in the Chair*

Regular Meeting, Nov. 30, 1943

Neurotic Disabilities in a Total War: The Rehabilitation of Patients with Neuroses. DR. WALTER S. MACLAY, London, England (by invitation).

In wartime the problem of the antisocial effect of neuroses has come much to the fore, whether the society concerned is the fighting services or the civilian community. Interest in psychosomatic illness has brought psychiatry into close relationship with social problems and social medicine. Psychiatrists are concerned with people who may be physically whole but who nevertheless are maladjusted to the community in which they live and who in that maladjustment show a variety of symptoms. A considerable number of medical and surgical patients who might be expected to be made well by the rehabilitation programs of medicine and surgery will be maladjusted and will not recover satsfactorily because of neurotic mechanisms. Therefore, psychiatrists have an important contribution to make in treatment centers, other than neurosis centers, in that rehabilitation in the full sense of the word has been the object of psychiatry for many years. Rehabilitation and treatment are, in fact, almost synonymous in psychiatric practice.

The importance of rehabilitation in its full sense, that is, the need to provide incentives to get well and the need to change the attitude of patients toward their illness, as well as the provision of occupation and physical training, was recognized early in the war in the neurosis centers of the emergency medical services, and they were the first to develop comprehensive schemes of treatment and after-care for both civilians and soldiers. In wartime more attention has to be given to the development of a sense of social responsibility through the organization and morale of the hospital than has to be given in peacetime, in that many of the patients are sent for treatment instead of applying it for themselves, with the result that the attitude of the patient is frequently one of pacificity, sometimes one of suspicion and occasionally one of resentment. Neurotic mechanisms operate against cooperation with the hospital where such cooperation stands for return to service or to the situation in which the patient broke down.

Patients must be made to feel that the hospital is not just a machine to get them back to the front. On the one hand, it must meet the needs of the individual; on the other, the needs of society. Patients who break down in wartime have to play a part in wartime society. They must not escape into too peaceful a setting but must be urged to a sense of social responsibility. With neurotic persons personal considerations are frequently apt to outweigh national needs. To force this issue, the neurosis centers are placed near cities liable to bombing, so that there is a background in which patients cannot escape from their war fears. Without immediate danger, there is an ever present sense of urgency, and the hospital is organized to preserve this. For example, fire-fighting squads and stretcher-bearer teams are organized among the patients, so that they are trained to work in spite of their symptoms.

Special psychiatric procedures as required individually are carried out against a background of occupational therapy, physical training, educational lectures, recreations and entertainments. The last two means of rehabilitation are as far as possible provided by the efforts of the patients themselves, and not from outside the hospital. The occupational work and physical training are much the same as in any other rehabilitation center and hospital, but the educational program deserves special attention. It has been developed with the cooperation of the Army Educational Corps and plays just as important a part among the men who are in the hospital as among those who are not. The lectures aim at mental stimulation with respect not only to circumscribed subjects but to social and political problems. Discussions are encouraged whenever possible, and the army scheme of devoting two hours a week to current affairs and citizenship has proved valuable.

Vocational Assessment.—In wartime a frequent cause of neurosis is maladjustment in the vocational sense, with attendant frustration and sense of futile endeavor. Proper vocational placement after treatment of the neurosis is one of the main stabilizing factors.

While the patient is under psychiatric care and treatment, the physician must decide for what type of work he will be suitable. The patient's performance in the general milieu already outlined provides some of the data for this assessment, but two other methods, to be indicated, give valuable help.

1. Psychologic testing. This procedure is carried out by close liaison between the physician and the nonmedical psychologist. The psychologic team investigates

clerical aptitudes or mechanical abilities in constructional work. These two fields are important in wartime, and the goal of treatment is adjustment in a wartime society. A bank clerk may be found to have high mechanical ability and will achieve success hitherto obstructed by a sense of failure, as an instrument maker or a laborer may be shown to have unsuspected abilities as a clerk or a draughtsman. 2. Technical classes and direct observation of performance. In order further to test the educational ability, a liaison has been achieved at some centers with a local technical institute whereby patients can attend courses in practical work, such as engineering, bookkeeping and typewriting. The reports from these technical institutes are of considerable value to the physicians and of great interest to the patients.

Vocational Placement.—Vocational assessment is useless without adequate placement. In the early stages of war it was difficult to achieve this for men in the forces, owing to administrative difficulties. The army has now introduced a scheme of transfer and special posting within the army, which is operated from the war office. The medical opinion is given, and suggestions are made with respect to suitable placement. The war office meets these suggestions through its special department, and the man is suitably posted. There is a constant liaison between the hospital and the branch of the war office concerned. The results have been satisfactory, and many men who would have broken down if returned to their previous duties are now giving satisfactory service. A follow-up investigation has confirmed the continued success of these men and has proved the satisfactoriness of the scheme.

For men who have to be discharged from the services and for civilians, every effort is made to see that their civilian job is as useful as possible and is vocationally suitable. This has been achieved by a liaison with the Ministry of Labour. A representative of this ministry attends the hospital each week and interviews all men and women, whether from the services or not, who are returning to civilian life. The representative has a medical report and the help of a social worker and advises each person in regard to future work and where it can best be found.

These two developments with the army and with the Ministry of Labour have done much to improve the morale of the hospital and further the rehabilitation of the patients. They are important in preventing invalidism and compensation claims.

NEW YORK ACADEMY OF MEDICINE. SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

CLARENCE P. OBERNDORF, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, Nov. 9, 1943

Presidential Address: The Nature of Psychogenic Cure. DR. C. P. OBERNDORF.

Integration of the Electroencephalogram: I. An Approach to Schizophrenia Through Electroencephalography. MR. CHARLES S. ROBERTS and DR. WILLIAM J. TURNER (by invitation).

The typical electroencephalographic record characteristic of schizophrenia is considered to be one of an unstable alternating current the zero potential of which is represented by a line drawn between the base lines established by the unactivated writing mechanism. Integration of areas above and below this line, by means of a polar planimeter, considered as the electronegative potential and the electropositive potential respectively, were carried out on 20 normal control subjects and 20 schizophrenic patients for a total of one hundred and eighty seconds for each group. Statistically significant differences were shown to exist in that in both occipital leads the average electronegative potential for the control subjects was reliably greater than that for the schizophrenic patients and the average electropositive potential for the schizophrenic patients was reliably greater than that for the normal subjects. In this report only one criterion of abnormality was employed in differentiation of schizophrenic and normal subjects, namely, the excess of electropositive potential over electronegative potential in the right occipital lead. The occurrence of only one abnormal interval in a record led to its classification as "questionable." By the application of this criterion, 75 per cent of the patients' electroencephalograms would be classified as "abnormal," 15 per cent as "questionable" and 10 per cent as "normal." Of the control electroencephalograms, 20 per cent would be classified as "abnormal," 15 per cent as "questionable" and 65 per cent as "normal."

Physiologic and Clinical Aspects of the Electroencephalogram. DR. TRACY J. PUTNAM and DR. PAUL F. A. HOEFER.

The significance of the frequency and pattern of the potentials recorded in the clinical electroencephalogram is discussed in correlation with possible underlying physiologic mechanisms and with experimental data obtained in observations on the origin of brain potentials, their conduction in the large projection systems of the cortex and their role in convulsive seizures.

The definition of normal activity is practical but arbitrary. Fourier's analysis has shown that the electroencephalograms of normal subjects and those of patients form a continuous "spectrum" of frequencies, from less than 1 up to 60 per second, with several maximums denoting an energy output larger with some frequencies than with others. However, no frequency as such is abnormal or significant of a specific clinical condition.

Gross departures from the normal pattern, at times to the point of obliteration of all normal activity, occur in various directions.

Slow activity is often seen associated with conditions in which the metabolism of the brain cells is depressed, as in sleep, anesthesia and coma, as a result of anoxia, lack of dextrose and disturbances in the intermediary dextrose metabolism. Slow activity may occur in states of impaired consciousness, but it does not necessarily signify an abnormal psychologic state; on the contrary, it may coincide with notable improvement during shock therapy.

Rapid activity, on the other hand, may occur in conditions in which the activity of cerebral neurons is increased, as in responses to sensory stimuli or in convulsive seizures. Normal subjects with intense mental activity, as well as persons in tense states, and patients with anxiety states and certain psychoses often show conspicuous rapid activity in the electroencephalogram.

It should be kept in mind that depression of metabolic function may precipitate an increase in cerebral activity under a variety of conditions and that impaired consciousness and increased neuronal activity are compatible.

Abnormally slow and abnormally rapid activity, though they occur with great regularity during certain types of convulsive manifestations, cannot be considered pathognomonic for these conditions in the interval record, though the existence of such activity, other known causes being eliminated, is often indicative or suggestive of these states. However, the abrupt appearance of high voltage, synchronized activity, especially of spike and wave activity, is reasonably certain evidence of a paroxysmal state.

Patterns and frequencies of brain potentials of experimental animals are quite similar to those seen in the human electroencephalogram. Experimental evidence exists to show that part of the normal activity during rest and potentials appearing during seizures originate in different cell layers of the cortex. Various anesthetics cause different patterns in the electroencephalogram taken during rest, and electrical stimulation supplemented by the use of convulsant drugs leads to slightly different patterns of activity. All of them, however, result in conducted axonal "spike" activity. The existence of complex neuronal chains with a number of synaptic barriers must be assumed in order to explain the spreading of rest potentials and seizure discharges from one side to the other and the facilitation of convulsive movement.

DISCUSSION ON PAPERS BY MR. ROBERTS AND DR. TURNER AND DRS. PUTNAM AND HOEFER

DR. BERNARD L. PACELLA: The paper by Mr. Roberts and Dr. Turner contains much that is interesting and thought provoking. One might evaluate the substance of the presentation from three points of view: first, the clinical material utilized; second, the actual data presented, and, third, the interpretation of these data in the light of the clinical material.

First, one wonders whether the choice of schizophrenic material does not carry with it a certain amount of error. The authors mentioned the paranoid, hebephrenic and catatonic forms of dementia precox. Patients with each of these forms of the disease vary significantly in their quantitative and qualitative expressions of psychologic phenomena and in concomitant physiologic changes throughout the body from patients with the other forms. For instance, the electroencephalograms of patients whose illness is classified as paranoid schizophrenia show an unusual incidence of normal records. On the other hand, the records of catatonic patients present a high incidence of conspicuously abnormal features, as was indicated in 3 of the cases studied by the authors. Furthermore, studies on cutaneous resistance have indicated that patients classified as hebephrenic exhibit a high cutaneous resistance as compared with normal control subjects. This in itself, incidentally, might result in attenuation of voltages emanating from the cortex and picked up through the scalp, and might even explain in part the character of the cumulative distribution curves shown by the authors. It is known that patients classified as paranoid usually differ substantially from patients with the catatonic and hebephrenic forms of the disease in certain constitutional endowments, particularly with regard to habitus and immunity or resistance to various diseases. This might imply a number of basic physiologic differences in these groups. Therefore, it might be preferable to employ for electrophysiologic study patients who represent as nearly as possible pure reaction types, such as those who exhibit only paranoid reactions, with approximately similar patterns of behavior and sensorial states. This would tend to enhance the validity of any statistical data obtained.

The data obtained by Dr. Turner and Mr. Roberts may be briefly considered. I understand that they employed the mechanical planimeter rather than an electronic variation of it; if so, they must be complimented on carrying out so arduous a task as that involved in following carefully the tracings of the brain waves. I did not note whether they repeated the same maneuver on the same electroencephalographic tracings to determine the standard error of deviation, which might be significantly high; possibly this was determined and found to be inconsequential.

From the work of Mr. Charles Sheer and Dr. John Lynn, at the Neurological Institute, with respect to the methodologic significance of the energy concept in experimental psychophysiology it appears that there are objections to the use of the terms "negative and positive energy" and "output" and "input." In measuring the area between the line of zero potential and the wave tracings, one is merely summating voltages, not dealing with energy values as such. To determine energy output one must square the voltage, as emphasized by Mr. Sheer and Dr. Lynn; thus, in the formula indicated by the authors by which they determine the number of microvolts per second, only the potential per unit of time is expressed. Energy must be expressed in terms of microvolt (squared) seconds, not as microvolts per second. I might add that one ordinarily does not speak of negative energy—energy is usually plotted as a unidirectional force, not as a phasic force. Squaring negative electropotential yields positive energy. A good deal of confusion and error could be avoided if the terms "electronegative potential" and "electropositive potential" were utilized more generally, rather than the terms "negative energy" and "positive energy," or, for that matter, "output" and "input."

My discussion relating to the concept of energy is derived principally from the work of and opinions expressed by Mr. Sheer and Dr. Lynn, who have been much interested in this aspect of electrophysiology, and whose work has been extremely enlightening.

In utilizing any apparatus, such as the electroencephalograph, for fine determinations of energy output, one must take into account the possible sources of error in the apparatus itself. For instance, unless special features were incorporated in the apparatus used by Dr. Turner and Mr. Roberts, the diaphragm to which the writing stylus was attached was not adjusted so that it would give perfectly linear tracings with varying voltages. To avoid actual errors in calculation, it might be necessary to run through the apparatus energy of known quantity and form and then to determine the degree to which this is distorted. In this way one could deal with energy values obtained from experimental sources.

I should be particularly interested in knowing the variations in cutaneous resistances for the various patients and for the controls, although I am aware that the authors mentioned the average figure of 10,000 ohms. For instance, I am told that Dr. Moldaver, in the course of his work on chronaxia, found differences in cutaneous resistances of from 5,000 to 75,000 ohms. It is conceivable that such variations might alter in some degree the data obtained by the authors.

From the data which Mr. Roberts and Dr. Turner presented, one important point stands out—the schizophrenic patients and the controls show a significant difference in the electronegative and the electropositive

voltages obtained over the right occipital region. This observation is an interesting one and should be examined further with larger series of patients. However, it would be wrong to draw generalizations on the basis of these data. That bursts of serial slow waves are observed characteristically, for instance, with convulsive disorders does not tell why they occur, or even what their nature is.

If further work along these lines should eventually verify the authors' observations with regard to a high electropositive potential and a low electronegative potential over the right occipital region in schizophrenic patients, three questions must still be considered: First, is this phenomenon an electrophysiologic expression of a basic disturbance or disease process which, at the same time, shows certain characteristic phenomena in the psychologic sphere; second, is it a psychosomatic expression of a primarily determined psychologic disturbance, or, third, is it merely an expression of a certain type of constitutional endowment in persons in whom certain forms of schizophrenia are likely to develop?

Mr. Roberts and Dr. Turner have undertaken an excellent type of investigation of the psychiatric disorders, and it is hoped that this kind of work will continue.

Dr. Putnam and Dr. Hoefer have admirably presented a number of important generalizations which do much to clarify the application of electroencephalographic evidence to clinical material. It is particularly gratifying to note the emphasis they have placed on the lack of specificity of electroencephalographic patterns for various clinical conditions; for practical purposes, however, much of this lack of specificity may be obviated by one's knowing the age and the clinical history and symptoms of the patient. For instance, an extremely abnormal record would have quite a different significance in the case of a patient who is stuporous and in the case of one whose sensorium is clear. A 7 per second rhythm might have entirely different meanings in relation to the 70 and to the 30 year old patient. Therefore, in an electroencephalographic report one might include not only a summary of the actual waves and frequencies noted and a statement as to whether the record appears to be abnormal or not, but a clinical correlation between the type and degree of abnormality and the clinical history. In this way, by utilizing the history and symptoms in the light of his electroencephalographic observations, the electroencephalographer can be of greatest value.

The authors stated that slow activity in the electroencephalogram does not necessarily signify abnormal psychologic states, but may coincide with notable improvement during shock therapy. This is especially true of patients with severe depressive states, in whom a half-dozen electric shock treatments may produce remarkable clearing of the depression; at the same time, however, there often develops a temporary and partial memory defect, in addition to a possible mild confusional state, which usually seems to be related to the appearance of the slow waves in the electroencephalogram. The illustration of a patient receiving electric shock therapy may therefore not be the best that could have been used. The authors stated that rapid activity is commonly seen in the electroencephalograms of normal persons in tense states, as well as during intense mental activity, and in patients with anxiety states. I might, perhaps, take slight exception to part of this statement. I have been impressed by the differences in the electroencephalograms of clinically normal subjects who exhibited mild apprehension or anticipatory tension and those of psychoneurotic patients who manifested a great deal of morbid anxiety. With the latter group I have frequently noted a high incidence of alpha rhythm of high amplitude and practically no fast activity, whereas subjects who were concentrating or were only mildly apprehensive with regard to the test procedure tended to show obliteration of the alpha rhythm. Now, whether the remaining low voltage, irregular activity consisted of newly developed fast activity related to tenseness or was merely what remained of the record, after obliteration of alpha rhythm, is difficult to say.

The utilization of electroencephalograms for the study of pathways in the brain and the functional relations between pathways and neuronal groups is excellently demonstrated by Dr. Putnam and Dr. Hoefer. One must feel indebted to these investigators for further clarification of the possible mechanism involved in the convulsive seizure. They mentioned that the subliminal activity in layer 5 of the cortex may act as a conditioning influence on the effector systems, which originate in part in that layer. In this connection, one may suggest as a possible substantiating bit of evidence the common observation of prominent alpha rhythm of high amplitude in adult epileptic patients, often when evidence of serial slow activity is lacking. It is unusual to observe only low voltage, irregular fast activity in the electroencephalogram of the average epileptic patient in his seizure-free periods. It is possible, therefore, that the prominent, high amplitude alpha rhythm does represent a conditioning influence or a facilitative factor for the convulsive discharge.

DR. WILLIAM J. TURNER: In working up these data Mr. Roberts and I of course endeavored in every way to anticipate questions which might be related to sources of error. We realize that we may not have avoided all such sources, and I thank Dr. Pacella for bringing up the matter of cutaneous resistance, which we did not measure. We felt, however, that cutaneous resistance was one of the constants which under the conditions of electroencephalography would cancel out. Our patients have been too few to justify our classifying them under reaction types. It might be of interest to mention that we had 1 patient who exhibited considerable blocking and manifested a pure hebephrenic reaction. We studied him some months later, after he had shown spontaneous improvement. His record at the time he was first examined showed four abnormal intervals. When he was ready to go home, no such interval was apparent. Repeated measurements of these areas in the same curve have shown that sigma was in the neighborhood of 0.1, which makes all the measurements except those in the left hemisphere significant. Although it is true that one should use the terms electropositive and electronegative, the fact is, whether the voltage is squared or not, the current is still a form of energy. Since the current is an alternating one, not "resistance" but "inductance" and "impedance" should be used. We feel that the definition of terms is a matter for the future. We have inserted a calibration made by the manufacturers and have shown that, if anything, the figures we obtained were weighted toward electronegativity, rather than toward electropositivity. We wish to thank Dr. Pacella again for pointing out sources of possible error.

DR. TRACY J. PUTNAM: I do not think I can add anything to Dr. Pacella's excellent review of the subject. I have great appreciation for the ingenious method which Dr. Turner has utilized in analyzing his records.

I may say that Dr. Hoefer and I have tried to think of all the ways in which electroencephalographic records might be treated mathematically. One might measure the total energy involved, or, as Dr. Turner has done, one might contrast the energy exerted in the negative with that exerted in the positive phase of the current. Or one might try to determine the proportion of variations from the basic frequency. In the present state of knowledge one can do no more than guess which of the many mathematical treatments of this curve will prove fruitful. As to Dr. Turner's results in the clinical cases, we have no contribution to make to the discussion, for our material does not include an appreciable number of psychotic patients.

Our work represents, I think, an attempt rather than an accomplishment. We endeavored this evening to present a point of view, rather than a systematized body of facts. It is interesting to look back on the beginning of electroencephalographic investigation and contrast it with the origin and development, for example, of electrocardiography. The electrocardiogram was analyzed in physiologic terms before it was introduced into clinical practice. It was quite different with the electroencephalogram. From the beginning there has been an empiric body of data, on the basis of which investigators have intuitively recognized certain patterns and have made some rather crude measurements. It seemed to us high time that some one analyze the electroencephalographic record in physiologic terms and study the point of origin, the physical principles, of the production of waves in the cortex and the pathways over which they are propagated.

INDEX TO VOLUME 51

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

Abnormalities and Deformities: See under names of organs and regions, as Corpus Callosum; Cranium; etc.
Abscess: See under names of organs and regions, as Brain, abscess; Medulla Oblongata; Spinal Cord; etc.
Acetylcholine: See Choline and Choline Derivatives; Dementia Praecox
Acid, Amino: See Amino Acids
  Glutamic: See also Epilepsy
  glutamic; effect of glutamic acid and other amino acids on maze learning in white rat, *446
Acid-Base Equilibrium, biochemical aspects of glutamic acid therapy for epilepsy, *393
  simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Adams, R. D.: Pathologic features of herpes zoster; note on "geniculate herpes," *216
Adelstein, L. J.: Tumor of acoustic nerve within petrous bone; operative removal, *268
Adler, A.: Disintegration and restoration of optic recognition in visual agnosia; analysis of case, *243
Adolescence, regular 40 to 50 day cycle of psychotic behavior in 14 year old boy, *478
Adrenal Preparations, action of adrenalin on transmission in sympathetic ganglia, which may play part in shock, 90
  delirium; reversibility of electroencephalogram with experimental procedures, *378
Adrenalin: See Adrenal Preparations
Age incidence of atrophy of olfactory nerves in man; contribution to study of process of ageing, 192
  Old: See Old Age
Agnosia: See Vision, defective
Aird, R. B.: Protective barriers of central nervous system; experimental study with trypan red, *54
Akelaitis, A. J.: Atrophy of basal ganglia in Pick's disease; clinicopathologic study, *27
Albumin: See Cerebrospinal Fluid
Alcoholism, nonconvulsive electric (faradic) shock therapy of psychoses associated with alcoholism, drug intoxication and syphilis, 199
  study of personalities of 289 abnormal drinkers, 469
  tremor and Babinski sign in alcoholic patients; incidence and interpretation, *403
Alexander, F.: Fundamental concepts of psychosomatic research; psychogenesis; conversion; specificity, 208
Alpers, B. J.: Aneurysm of vertebral artery; report of case in which aneurysm simulated tumor of posterior fossa, *271
  Site of origin of fasciculations in voluntary muscle, *264
Amentia: See Feeblemindedness; Insanity; Mental Diseases; etc.
Amino Acids, effect of glutamic acid and other amino acids on maze learning in white rat, *446
Amphetamine, Therapy: See Dementia Praecox; Migraine
Anderson, F. M.: Tumor of acoustic nerve within petrous bone; operative removal, *268
Anderson, G. C.: Racial and sexual incidence of primary intracranial tumors; statistical study of 133 cases verified by autopsy, *564
Androgens, testosterone therapy of male eunuchoids; sublingual administration of testosterone compounds, 290
  therapy for involutional melancholia, *457
Anesthesia, electronarcosis in animals and in man, *232
  procaine nerve block in investigation of peripheral nerve injuries, 97
  sensory reception in hysterical anesthesia as measured by cold pressor response, *84
Anesthetics: See Anesthesia
Aneurysm, intracranial, 577
  of vertebral artery; report of case in which aneurysm simulated tumor of posterior fossa, *271
  progressive multiform angiosis; association of cerebral angioma, aneurysms and other vascular changes in brain, *182
  rupture of aneurysm of circle of Willis; relationship between intraocular and intracranial hemorrhage, 488
Angioma, progressive multiform angiosis; association of cerebral angioma, aneurysms and other vascular changes in brain, *182
Angiospasm: See Brain, blood supply
Anhalonium; peyote intoxication, 408
Anhedonia, constitutional, and social neurosis, 497
Anomalies: See under names of organs and regions
Anoxemia: See under Blood; Oxygen, deficiency
Anoxia: See Oxygen, deficiency
Anxiety: See Neuroses and Psychoneuroses
Aorta, syphilis; neuritides accompanying syphilitic aortitis, 99
Aortitis, Syphilitic: See Aorta, syphilis
Apoplexy: See Brain, hemorrhage
Apparatus: See also Instruments
  electrofit in treatment of mental disease, 411
  pain threshold in man, 285
  simple automatic pneumoencephalograph, *405
Arachnoid, inflammation; chronic tuberculous cerebrospinal leptomeningitis, 198
  inflammation; optochiasmic arachnoiditis, 410
Arieff, A. J.: Electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
Arieti, S.: Progressive multiform angiosis; association of cerebral angioma, aneurysms and other vascular changes in brain, *182
Armed Forces Personnel: See Aviation and Aviators; Military Medicine; etc.
Arteries: See also Aneurysm; Aorta; Blood pressure; Embolism; Thrombosis; Vasomotor System; etc.
  aneurysm of vertebral artery; report of case in which aneurysm simulated tumor of posterior fossa, *271
  Cerebral: See Brain, blood supply
  Retinal: See Retina, blood supply
Arthritis, neurologic and endocrine aspects of atrophic arthritis (deformans), 491
Artificial Fever Therapy: See Neurosyphilis
Arzt, P. K.: Abscess within spinal cord; review of literature and report of 3 cases, *533
Ascroft, P. B.: Neurosurgical experience in Egypt and Libya, 295
Atrophy: See also under names of organs and regions, as Brain, atrophy; Cerebellum; Nerves; etc.
  muscular: studies of neuromuscular disorders; myogram, blood cholinesterase and effects of prostigmine in myasthenia gravis and progressive muscular atrophy, 490
Aviation and Aviators, psychiatry in field of aviation medicine, 493
Avitaminoses: See under Vitamins
Axons: See Neurons

Babinski Sign: See Reflex
Backache, herniation of nucleus pulposus as complication of pre-existing low back instability, 489
Barré-Guillain Syndrome: See Nerves, roots
Barrera, S. Eugene, appointment of, 414
Behavior, Children's: See under Children
Bell's Palsy: See Paralysis, facial
Benzedrine: See Migraine
Berger Rhythm: See Brain, electroencephalography
Beverages, Alcoholic: See Alcoholism

Biliary Tract, effect of sectioning various autonomic nerves on rate of emptying of biliary tract in cat, 194
Binger, C.: Psychodynamic study of group of patients suffering from arterial hypertension, 100
Blindness: See Vision, defective
Night Blindness: See Night Blindness
Blood, biochemical studies on patients with schizophrenia; dextrose, oxygen and carbon dioxide contents of arterial and venous blood from cranial cavity, *469
Circulation: See also Arteries; Cardiovascular System; Heart; Vasomotor System; etc.
circulation; effects of increased intraventricular pressure on respiration and circulation, *514
pressure; effect of variations in subarachnoid pressure on venous pressure in superior longitudinal sinus and in torcular of dog, 90
pressure, high; occurrence of peripheral facial paralysis in hypertensive vascular disease, 288
pressure, high; psychodynamic study of group of patients suffering from arterial hypertension, 100
pressure, high; treatment of essential hypertension by sympathectomy, 201
studies of neuromuscular disorders; myogram, blood cholinesterase and effects of prostigmine in myasthenia gravis and progressive muscular atrophy, 490
Sugar: See also Dextrose; Insulin; etc.
sugar; acetylcholine level of rat cerebral cortex under conditions of anoxia and hypoglycemia, 487
transfusion; delirium; reversibility of electroencephalogram with experimental procedures, *378
transfusion; effect of serum on survival time of brain tissue and revival of cerebral oxidation, *176
Blood-Brain Barrier: See Hemoencephalic Barrier
Body, Mind and Body: See under Mind
Bond, E. D.: Replacement of convulsive attacks by psychoses, 205
Bones, eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452

Book Reviews:
Behavior and Neurosis; J. H. Masserman, 300
Boy Sex Offender and His Later Career; L. J. Doshay, 211
Contemporary Psychopathology; edited by S. S. Tompkins, 302
Convulsive Seizures: How to Deal with Them; Manual for Patients, Their Families and Friends; T. J. Putnam, 212
Development in Adolescence; H. E. Jones, 304
Introduction to Group Therapy; S. R. Slavson, 110
Lincoln — Douglas: Weather as Destiny; W. F. Petersen, 303
Manual of Industrial Hygiene and Medical Service in War Industries, Prepared by Division of Industrial Hygiene, National Institute of Health, United States Public Health Service; W. M. Gafafer, 212
Medicine and War; edited by W. H. Taliaferro, 414
Mind: Perception and Thought in Their Constructive Aspects; P. Schilder, 303
Nature and Treatment of Mental Disorders; D. T. V. Moore, 112, 499
Neurologia ocular; E. Adroqué, 304
Physiological Psychology; C. T. Morgan, 111, 499
Psychiatric Novels of Oliver Wendell Holmes; C. P. Oberndorf, 301
Rehabilitation of War Injured: Symposium; edited by W. B. Doherty and D. D. Runes, 111
Techniques of Self-Help in Psychiatric Aftercare: Developed by Recovery, Inc., the Association of Former Patients; A. A. Low, 302
What Is Hypnosis? Studies in Conditioning; A. Salter, 500
Women in Wartime, 304

Boutons: See Neurons
Brachium Pontis: See Cerebellum
Brain: See also Cerebellum; Corpus Callosum; Dura Mater; Hypothalamus; Medulla Oblongata; Meninges; Nervous System; Thalamus; etc.
Brain—Continued
acetylcholine level of rat cerebral cortex under conditions of anoxia and hypoglycemia, 487
acid-soluble phosphorus compounds of cerebral tissue, 89
afferent areas in brain of ungulates, 487
anatomicoclinical report of case of carbon monoxide poisoning, with survival for 49 years; correlation of evolution of extrapyramidal symptoms and structural organization of motor pathways of forebrain, 494
atrophy; atrophy of basal ganglia in Pick's disease; clinicopathologic study, *27
atrophy; hemiatrophy of brain with contralateral cerebellar atrophy, 577
biopsies of brain of schizophrenic patients and experimental animals, *155
Blood Supply: See also Aneurysm; Arteries; Hemoencephalic Barrier; etc.
blood supply; progressive multiform angiosis; association of cerebral angioma, aneurysms and other vascular changes in brain, *182
cerebral and spinal operations in case of severe postencephalitic tremors, 108
cerebral arteriovenous oxygen difference; mental deficiency, *73
cerebral cortex of man with senile dementia believed to be 107 years old, *78
cerebral metabolism in hypoxia, *472
cyst, colloid, of third ventricle, *570
cysts; agenesis of corpus callosum with possible porencephaly; review of literature and report of case, *35
cysts, paraphysial, of third ventricle, 95
cytoarchitecture of individual parietal areas in monkey (Macaca mulatta) and distribution of efferent fibers, 88
development of human mesencephalic trigeminal root and related neurons, 87
developmental control of pars intermedia by, 193
Diseases: See also Encephalitis; Insanity; Mental Diseases; etc.
diseases; homolateral reflex exaggeration after brain-stem lesion, 286
disintegration and restoration of optic recognition in visual agnosia; analysis of case, *243
effect of serum on survival time of brain tissue and revival of cerebral oxidation, *176
effects of variations in intracranial pressure, *508
electroencephalogram as diagnostic aid, 206
electroencephalographic study of 275 candidates for military service, 577
electroencephalography; clinical and electroencephalographic observations in severe epilepsy under treatment, 92
electroencephalography; clinical observations on patients with behavior disorders who show abnormal electroencephalograms, 206
electroencephalography; delirium; electroencephalographic data, *356
electroencephalography; delirium; reversibility of electroencephalogram with experimental procedures, *378
electroencephalography, diagnostic value of, 203
electroencephalography; effect of hypothalamic lesions on electrical activity of cerebral cortex, 286
electroencephalography; effect of pneumoencephalographic tests on epilepsy as proved by electroencephalograms, 96
electroencephalography; effects on electroencephalogram of chronic lesions of basal ganglia, thalamus and hypothalamus of monkeys, 487
electroencephalography; integration of electroencephalogram; approach to schizophrenia through electroencephalography, 581
electroencephalography; physiologic and clinical aspects of electroencephalogram, 581
electroencephalography; relation of narcolepsy to epilepsies; clinical-electroencephalographic study, *163
electroencephalography; simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452
functional development of fetal brain, 285

Brain—Continued
functional organization of temporal lobe of monkey (Macaca mulatta) and chimpanzee (Pan satyrus), 287
hemorrhage; acute craniocerebral trauma, 410
hemorrhage; disorientation and associated Gerstmann syndrome from intracerebral hemorrhage, 93
hemorrhage; fatal intracranial venous hematoma following ventricular drainage, 94
human pyramidal tract; effect of paralysis produced by cerebral tumors on axons of pyramids, *213
Inflammation: See Encephalitis
Injuries: See also Head, injuries
injuries; treatment of cerebral contusion, 292
Localization of Function: See also Brain, diseases; Brain, tumors
localization of function; discharges from vestibular receptors in cat, 194
localization of function; new answer to question of macular sparing, 575
localizing value of clinical, electroencephalographic and pneumoencephalographic findings in epilepsy, 293
long association fibers in cerebral hemispheres of monkey and chimpanzee, 287
movements of locomotion in decerebrate cat, 195
Physiology: See Brain, electroencephalography; Brain, localization of function
role of cortical respiratory center in production of respiratory distress during electric shock therapy, 205
Sclerosis: See Sclerosis
simple automatic pneumoencephalograph, *405
suppression of motor response in man, *528
surgery; bilateral prefrontal lobotomy, 576
surgery; bilateral prefrontal lobotomy; perspective and recent survey of results, 202
surgery; neurosurgical experience in Egypt and Libya, 295
surgery; prefrontal lobotomy in chronic psychoses, 200
surgery; prefrontal lobotomy in treatment of mental disease, 578
surgery; prefrontal lobotomy in treatment of mental disease; surgical technic, 579
tumors, multiple, of diverse origin, 488
tumors; oligodendrogliomatosis of cerebrospinal pathway, 407
tumors; torular granuloma simulating cerebral tumor; report of 2 cases, *426
Brenner, C.: Paralysis of nerve induced by direct pressure and by tourniquet, *1
Brickner, R. M.: Visible retinal arteriolar spasm associated with multiple sclerosis; preliminary report, *573
Bucy, P. C.: Suppression of motor response in man, *528
Bunts, A. T.: Agenesis of corpus callosum with possible porencephaly; review of literature and report of case, *35

Calcium and Calcium Compounds, equilibrium between calcium and cephalin in various systems, 285
Cancer: See also Sarcoma; Tumors; etc.; and under names of organs and regions
incidence of metastases to nervous system, *423
Carbon Monoxide, poisoning; anatomicoclinical report of case with survival for 49 years; correlation of evolution of extrapyramidal symptoms and structural organization of motor pathways of forebrain, 494
Cardiazol: See Dementia Praecox
Cardiovascular System: See also Arteries; Heart; Vasomotor System; etc.
acute cardiovascular collapse after insulin shock treatment, 93
fatal circulatory failure caused by electric shock therapy, *557
Case, T. J.: Diagnostic value of electroencephalography, 203
Catalepsy, experimental, produced by nicotine, 196
Cataplexy and its treatment, 491
Catatonia: See Dementia Praecox
Cauda Equina: See Spinal Cord
Causalgia: See Neuralgia
Caveny, E. L.: Psychiatry in field of aviation medicine, 493
Cephalalgia: See Headache
Cephalin: See Lipoids
Cerebellum, atrophy, 94
atrophy; hemiatrophy of brain with contralateral cerebellar atrophy, 577
cerebellar extradural hematoma, 94
cerebellar syndrome following heat stroke, *67
Localization of Function: See Brain, localization of function
Cerebrospinal Fluid, 199
albuminocytologic dissociation in spinal fluid with xanthochromia, 97
encephalomyeloradiculitis, 198
Guillain-Barré syndrome; early diagnosis, 288
Cerebrum: See Brain
Chaffee, J. S.: Agenesis of corpus callosum with possible porencephaly; review of literature and report of case, *35
Chemotherapy: See Meningitis
Chiasm, Optic: See Optic Chiasm
Children, clinical observations on patients with behavior disorders who show abnormal electroencephalograms, 206
prognosis in schizophrenic-like psychoses in, 407
psychic deafness in, *544
Cholesterol: See Lipoids
Choline and Choline Derivatives, acetylcholine level of rat cerebral cortex under conditions of anoxia and hypoglycemia, 487
effect of prostigmine and acetylcholine on denervated muscle, 406
removal of acetylcholine by cholinesterase injections and effect thereof on nerve impulse transmission, 487
synthesis of acetylcholine in sympathetic ganglia and cholinergic nerves, 90
Cholinesterase and behavior problem in Amblystoma, 406
Chordotomy: See under Spinal Cord
Chorea complicating polycythemia vera, 93
Choriomeningitis, relationship between benign lymphocytic meningitis and poliomyelitis, 197
Circle of Willis: See Aneurysm
Circulatory System: See Cardiovascular System; Heart
Cisterna Magna, effects of variations in intracranial pressure, *508
Climacteric: See Menopause
Coburn, F. E.: Psychopharmacologic study of schizophrenia and depressions; intravenous administration of sodium amytal and amphetamine sulfate separately and in various combinations, *260
Cochlea: See Ear, internal
Cocoanut Grove Fire, disintegration and restoration of optic recognition in visual agnosia; analysis of case, *243
Cohen, L. H.: Acetylcholine treatment of schizophrenia, *171
Cohn, R.: Relation of narcolepsy to epilepsies; clinical-electroencephalographic study, *163
Cold, epileptiform attacks produced by sudden cooling of frog spinal cord, 286
sensory reception in hysterical anesthesia as measured by cold pressor response, *84
use of refrigeration therapy in mental disease with report of 16 cases, 290
Colleges: See Universities
Coma: See Dementia Praecox; Insulin
Communicable Diseases: See Meningitis; etc.
Conditioned Reflexes: See under Reflex
Congress: See Societies
Conjunctivitis; encephalitis following inclusion conjunctivitis, 96
Consciousness, effect of raised intracranial pressure on, *508
Constitution; constitutional anhedonia and social neurosis, 497
Contusion: See Brain, injuries
Convulsions: See also Epilepsy
analysis of convulsive movements by slow motion pictures, 298
anatomic and pathologic considerations in convulsive disorder, 487
effect of electrically and chemically induced convulsions on conditioned reflexes, 285
replacement of convulsive attacks by psychoses, 205
Cornea, experimental studies on development of corneal reflex in amphibia; influence of periphery on reflex center, 193

Corpus Callosum, agenesis with possible porencephaly; review of literature and report of case, *35
Corpus Geniculatum, structural changes in external geniculate body of rat following removal of eyes, 575
Corpus Luysi: See Hypothalamus
Corticospinal Tract: See Pyramidal Tract
Cotton, H. A.: Psychiatric problems in military service, 493
Cranium: See also Head; Temporal Bone
Abnormalities: See also Microcephaly
abnormalities; operation for scaphocephaly, 578
biochemical studies on patients with schizophrenia; dextrose, oxygen and carbon dioxide contents of arterial and venous blood from cranial cavity, *469
effect of bone dysplasia on cranial nerves in vitamin A-deficient animals, 90
effect of raised intracranial pressure on consciousness, *508
effects of increased intraventricular pressure on respiration and circulation, *514
effects of variations in intracranial pressure, *508
Injuries: See Brain, injuries; Head, injuries
osteochondromas arising from base of skull, 95
plastic repair of defects of skull, 202
pressure; effect of variations in subarachnoid pressure on venous pressure in superior longitudinal sinus and in torcular of dog, 90
pressure; fatal intracranial venous hematoma following ventricular drainage, 94
racial and sexual incidence of primary intracranial tumors; statistical study of 133 cases verified by autopsy, *564
Cretinism, cerebral arteriovenous oxygen difference; mental deficiency, *73
Crime and Criminals: See Jurisprudence, Medical; etc.
Cruvant, B. A.: Relation of narcolepsy to epilepsies; clinical-electroencephalographic study, *163
Curare, use of strychnine in curare-aided metrazol treatment of psychoses, 200
Cysts: See under names of organs and regions, as Brain; etc.

Danziger, L.: Androgen therapy for involutional melancholia, *457
Specific treatment of psychosis due to estrogen deficiency, *462
Deafness, psychic, in children, *544
Defectives: See Feeblemindedness
Delirium: See also Insanity
electroencephalographic data, *356
reversibility of electroencephalogram with experimental procedures, *378
Delusions: See under Dementia Praecox; Insanity; etc.
Dementia: See also Dementia Paralytica; Dementia Praecox; Insanity; etc.
cerebral cortex of man with senile dementia believed to be 107 years old, *78
Dementia Paralytica: See also Neurosyphilis
electric shock treatment in general paresis, 200
nonconvulsive electric (faradic) shock therapy of psychoses associated with alcoholism, drug intoxication and syphilis, 199
Dementia Praecox, acetylcholine treatment of schizophrenia, *171
biochemical studies on patients with schizophrenia; dextrose, oxygen and carbon dioxide contents of arterial and venous blood from cranial cavity, *469
biopsies of brain of schizophrenic patients and experimental animals, *155
catamnesis of patients submitted to insulin therapy, 292
clinical studies in schizophrenia, 407
comparison of schizophrenia and manic-depressive disorders with reference to emotional maturity, 92
environmental and personality factors in psychoses, 576
integration of electroencephalogram; approach to schizophrenia through electroencephalography, 581
prognosis in schizophrenic-like psychoses in children, 407
prolonged insulin coma in treatment of schizophrenia, *550
Dementia Praecox—Continued
psychopharmacologic study of schizophrenia and depressions; intravenous administration of sodium amytal and amphetamine sulfate separately and in various combinations, *260
significance of psychologic research in schizophrenia, 407
Denny-Brown, D.: Paralysis of nerve induced by direct pressure and by tourniquet, *1
Pathologic features of herpes zoster; note on "geniculate herpes," *216
Depression: See also Insanity; Mental Diseases; Neuroses and Psychoneuroses
psychopharmacologic study of schizophrenia and depressions; intravenous administration of sodium amytal and amphetamine sulfate separately and in various combinations, *260
Dextrose: See also Blood sugar
delirium; reversibility of electroencephalogram with experimental procedures, *378
simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Diencephalon: See Brain
Diethylstilbestrol: See Estrogens
Dilantin: See Epilepsy
Diodrast: See under Spine
Diphenylhydantoinate: See Epilepsy
Diplegia: See Paralysis
Diplopia in narcolepsy, 488
Dipsomania: See Alcoholism
Disk, Intervertebral: See under Spine
Dl Alpha Tocopherol: See Vitamins, E
Drugs, Addiction: See also under names of drugs
addiction; nonconvulsive electric (faradic) shock therapy of psychoses associated with alcoholism, drug intoxication and syphilis, 199
Dumoff, E.: Cerebellar syndrome following heat stroke, *67
Dunning, H. S.: Injury to peroneal nerve due to crossing legs, *179
Dura Mater: See also Meninges
effect of variations in subarachnoid pressure on venous pressure in superior longitudinal sinus and in torcular of dog, 90
Dyskinesia: See Movements
Dysmorphopsia: See Vision, defective
Dystonia; clinical classification, *319
historical review; analysis of dystonic symptoms and physiologic mechanisms involved, *305
Dystrophy, Muscular: See Atrophy, muscular

Ear: See also Deafness
abscess of medulla oblongata; report of case, *282
internal; independent differentiation of sensory areas of avian inner ear, 89
size, development and innervation of labyrinth sensory areas in squalus, 88
Ecology: See Environment
Edema: See under names of organs and regions
Electricity: See Electrotherapy
Electrodiagnosis: See Muscles
Electroencephalogram: See Brain, electroencephalography
Electromyography: See Muscles
Electronarcosis: See Anesthesia
Electrotherapy: See also under diseases, organs and regions
effect of electrically and chemically induced convulsions on conditioned reflexes, 285
electric shock therapy applied to problems of epilepsy, 577
fatal circulatory failure caused by electric shock therapy, *557
fatalities associated with electric shock treatment of psychoses; report of 2 cases, with autopsy observations in 1 of them, *397
Embolism: See also Thrombosis
cerebral air embolism, 410
Emotions, comparison of schizophrenia and manic-depressive disorders with reference to emotional maturity, 92
fundamental concepts of psychosomatic research; psychogenesis; conversion; specificity, 208
loss of emotional expression and body scheme, 93

Encephalitis: See also Encephalomyelitis
cerebral and spinal operations in case of severe postencephalitic tremors, 108
epidemiologic aspects in Yakima Valley, Wash., 92
following inclusion conjunctivitis, 96
physical, psychiatric and psychometric studies of postencephalitic parkinsonism, 91
Encephalomyelitis, epidemiologic aspects of encephalitis in Yakima Valley, Wash., 92
Encephalopathy: See Brain, diseases
Encephalorrhagia: See Brain, hemorrhage
Engel, G. L.: Delirium; electroencephalographic data, *356
Delirium; reversibility of electroencephalogram with experimental procedures, *378
Simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Enucleation: See Eyes, surgery
Environment; environmental and personality factors in psychoses, 576
Eosinophils, eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452
Epidermoid: See Spinal Cord
Epilepsy: See also Convulsions
American Branch of International League Against Epilepsy, 579
biochemical aspects of glutamic acid therapy for, *393
clinical and electroencephalographic observations in severe epilepsy under treatment, 92
diagnostic value of electroencephalography, 203
effect of pneumoencephalographic tests on epilepsy as proved by electroencephalograms, 96
electric shock therapy applied to problems of, 577
electroencephalogram as diagnostic aid, 206
epileptiform attacks produced by sudden cooling of frog spinal cord, 286
evaluation of continued therapy with phenytoin sodium, 289
idiopathic, pitressin diagnosis of, 89
localizing value of clinical, electroencephalographic and pneumoencephalographic findings, 293
relation of narcolepsy to epilepsies; clinical-electroencephalographic study, *163
replacement of convulsive attacks by psychoses, 205
spinal injuries in shock and epileptic convulsions, 293
Equilibrium: See Cerebellum; Ear, internal; Posture; etc.
Acid-Base: See Acid-Base Equilibrium
Estrogens, specific treatment of psychosis due to estrogen deficiency, *462
Eunuchoidism, testosterone therapy of male eunuchoids; sublingual administration of testosterone compounds, 290
Exhibitionism: See Sex, perversion
Extrapyramidal Tract, anatomicoclinical report of case of carbon monoxide poisoning, with survival for 49 years; correlation of evolution of extrapyramidal symptoms and structural organization of motor pathways of forebrain, 494
Extremities: See also Arms; Legs
Paralysis: See also Paralysis; Poliomyelitis
paralysis, familial periodic, 103
paralysis; paralysis of nerve induced by direct pressure and by tourniquet, *1
sensory reception in hysterical anesthesia as measured by cold pressor response, *84
Eyes: See also Vision; and under special structures of eyes, i. e., Retina; etc.
experimental studies on development of corneal reflex in amphibia; influence of periphery on reflex center, 193
hemorrhage; rupture of aneurysm of circle of Willis; relationship between intraocular and intracranial hemorrhage, 488
paralysis; congenital paralysis of lateral rotators of eyes with paralysis of muscles of face, 578
surgery; structural changes in external geniculate body of rat following removal of eyes, 575

Face, Paralysis: See Paralysis, facial
Fat: See Lipoids
Fay, T.: Analysis of convulsive movements by slow motion pictures, 298
Fazekas, J. F.: Cerebral arteriovenous oxygen difference; mental deficiency, *73
Feeblemindedness: See also Idiocy
cerebral arteriovenous oxygen difference; mental deficiency, *73
Ferris, E. B., Jr.: Simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Fever, Therapeutic: See under Dementia Paralytica; Mental Diseases; Neurosyphilis; etc.
Filum Terminale: See Spinal Cord
Fingers and Toes, finger flexor reflex, *125
finger-thumb reflex (Mayer), *132
Fitzgerald, P. J.: Pathologic features of herpes zoster; note on "geniculate herpes," *216
Foramen, Intervertebral: See under Spine
Forebrain: See Brain
Forster, F. M.: Site of origin of fasciculations in voluntary muscle, *264
Franklin, C. R.: Visible retinal arteriolar spasm associated with multiple sclerosis; preliminary report, *573
Freeman, W.: Cerebellar syndrome following heat stroke, *67
Freis, E. D.: Eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452
Friedman, A. P.: Tremor and Babinski sign in alcoholic patients; incidence and interpretation, *403
Froeschels, E.: Psychic deafness in children, *544
Frostig, J. P.: Electronarcosis in animals and in man, *232
Furmethide, use in testing sweat secretion in man, *568

Gait: See Locomotion
Ganglion: See also Nervous System; Neurons
basal; atrophy of basal ganglia in Pick's disease; clinicopathologic study, *27
basal; effects on electroencephalogram of chronic lesions of basal ganglia, thalamus and hypothalamus of monkeys, 487
development of cranial sympathetic ganglia in cat, 87
geniculate; pathologic features of herpes zoster; note on "geniculate herpes," *216
Sympathetic: See also Nervous System
sympathetic; action of adrenalin on transmission in sympathetic ganglia, which may play part in shock, 90
sympathetic, synaptic potentials and transmission in, 91
Ganglionectomy: See Nerves, roots
Garol, H. W.: Suppression of motor response in man, *528
Geniculate Body: See Corpus Geniculatum
Gerstmann Syndrome: See Perception
Golseth, J. G.: Electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
Gonorrhea, polyneuritis following therapy with sulfonamide compound, 99
Gottlieb, J. S.: Psychopharmacologic study of schizophrenia and depressions; intravenous administration of sodium amytal and amphetamine sulfate separately and in various combinations, *260
Gralnick, A.: Fatalities associated with electric shock treatment of psychoses; report of 2 cases, with autopsy observations in 1 of them, *397
Granuloma, eosinophilic, of bone presenting neurologic signs and symptoms; report of case, *452
torular, simulating cerebral tumor; report of 2 cases, *426
Gray, E. W.: Progressive multiform angiosis; association of cerebral angioma, aneurysms and other vascular changes in brain, *182
Gudden Commissure: See Optic Chiasm
Gurdjian, E. S.: Cerebral metabolism in hypoxia, *472
Guttman, S. A.: Electromyography as method for determination of level of lesions in spinal cord, *415
Use of furmethide in testing sweat secretion in man, *568

Hand flexor reflex, *131
Hausman, L.: Bernard Sachs, 481

Haws, R. J.: Biochemical studies on patients with schizophrenia; dextrose, oxygen and carbon dioxide contents of arterial and venous blood from cranial cavity, *469
Head: See also Cranium
Injuries: See also Brain, injuries; etc.
injuries; acute craniocerebral trauma, 410
injuries; care on large scale, 296
injuries, evaluation of complaints after, 409
injuries; indirect injuries of optic nerve, 489
injuries; neurosurgical experience in Egypt and Libya, 295
retraction reflex, *124
Headache: See Migraine
Hearing: See Deafness
Heart: See also Blood, circulation; Cardiovascular System
fatal circulatory failure caused by electric shock therapy, *557
Heat, cerebellar syndrome following heat stroke, *67
Heath, R. G.: Role of cortical respiratory center in production of respiratory distress during electric shock therapy, 205
Heilbrunn, G.: Biopsies of brain of schizophrenic patients and experimental animals, *155
Heine-Medin's Disease: See Poliomyelitis
Hematoma: See under Cerebellum
Hemianopsia, homonymous; report of 2 unusual cases, 413
Hemiatrophy: See Brain
Hemiplegia: See also Brain, hemorrhage; Extremities, paralysis; Paralysis
in tuberculous meningitis, 196
Hemoencephalic Barrier, protective barriers of central nervous system; experimental study with trypan red, *54
Hemorrhage: See also Brain, hemorrhage; Eyes, hemorrhage; Meninges, hemorrhage; etc.
effects of morphine in experimental shock due to, 576
Hemostasis, paralysis of nerve induced by direct pressure and by tourniquet, *1
Herpes zoster, pathologic features; note on "geniculate herpes," *216
Herz, E.: Dystonia; clinical classification, *319
Dystonia; historical review; analysis of dystonic symptoms and physiologic mechanisms involved, *305
Himwich, H. E.: Cerebral arteriovenous oxygen difference; mental deficiency, *73
Hoefer, P. F. A.: Electromyography as method for determination of level of lesions in spinal cord, *415
Physiologic and clinical aspects of electroencephalogram, 581
Homesickness, cryptic nostalgia, 92
Hormones: See Estrogens; Insulin; etc.
Hughes, J.: Electroencephalogram as diagnostic aid, 206
Spinal shock, 298
Hydrocephalus, cerebral arteriovenous oxygen difference; mental deficiency, *73
Hyperhidrosis: See Sweat Glands
Hyperinsulinism: See under Insulin
Hyperpyrexia: See Dementia Paralytica; Mental Diseases; Neurosyphilis; etc.
Hypertension: See Blood pressure, high
Hypoglycemia: See Blood sugar; Insulin
Hypophysis: See Pituitary Body
Hypothalamus: See also Pituitary Body
effect of hypothalamic lesions on electrical activity of cerebral cortex, 286
effects on electroencephalogram of chronic lesions of basal ganglia, thalamus and hypothalamus of monkeys, 487
Hypoxia: See Oxygen, deficiency
Hysteria: See also Neuroses and Psychoneuroses and malingering in nurses, 207
fundamental concepts of psychosomatic research; psychogenesis; conversion; specificity, 208
sensory reception in hysterical anesthesia as measured by cold pressor response, *84

Idiocy: See also Feeblemindedness
cerebral arteriovenous oxygen difference; mental deficiency, *73
Mongolian: See Mongolism
Indians, American; peyote intoxication, 408
Inebriety: See Alcoholism
Infantile Paralysis: See Poliomyelitis
Infants, newborn; encephalitis following inclusion conjunctivitis, 96
Influenza, response of Pfeiffer's bacillus meningitis to sulfapyridine, 196
Infundibulum: See Hypothalamus
Injuries: See under Brain; Head; Nerves, optic; Spine; etc.
Insanity: See also Dementia; Dementia Praecox; Depression; Mental Diseases
Alcoholic: See Alcoholism
comparison of schizophrenia and manic-depressive disorders with reference to emotional maturity, 92
environmental and personality factors in psychoses, 576
manic-depressive psychoses among college students, 576
replacement of convulsive attacks by psychoses, 205
Instruments: See also Apparatus
paralysis of nerve induced by direct pressure (mercury pressure bag) and by tourniquet, *1
Insulin, acute cardiovascular collapse after insulin shock treatment, 93
catamnesis of patients with dementia praecox submitted to insulin therapy, 292
evaluation of effects of intravenous insulin technic in treatment of mental diseases, 200
prolonged insulin coma in treatment of schizophrenia, *550
treatment of psychoses with long protracted insulin coma, 199
Intelligence Tests: See Mental Tests
Intervertebral Disks: See under Spine
Intoxication: See Alcoholism

Jaw reflex, *124
Jefferson, G.: Care of head injuries on large scale, 296
Jetter, W. W.: Fatal circulatory failure caused by electric shock therapy, *557
Jurisprudence, Medical; pain threshold in man, 285

Kahn, A. J.: Effects of variations in intracranial pressure, *508
Katzenelbogen, S.: Biochemical studies on patients with schizophrenia; dextrose, oxygen and carbon dioxide contents of arterial and venous blood from cranial cavity, *469
Kenny Treatment: See Poliomyelitis
Kirschbaum, W. R.: Biopsies of brain of schizophrenic patients and experimental animals, *155
Knee Jerk: See Reflex, patellar

Labyrinth: See Ear, internal
Lambros, V. S.: Diagnostic value of electroencephalography, 203
Landry's Paralysis: See Paralysis, acute ascending
Larynx, paralysis of left recurrent laryngeal nerve following subcutaneous administration of antitetanic serum, 98
Lassek, A. M.: Human pyramidal tract; effect of paralysis produced by cerebral tumors on axons of pyramids, *213
Learning, effect of glutamic acid and other amino acids on maze learning in white rat, *446
Legs: See also Extremities
injury to peroneal nerve due to crossing legs, *179
Leptomeninges: See Meninges
Levin, A. G.: Eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452
Lipids: See Lipoids
Lipochromes; lipofuscin distribution in basal ganglia, 192
Lipofuscin: See Lipochromes
Lipoids: See also Phosphorus and Phosphorus Compounds
equilibrium between calcium and cephalin in various systems, 285
Lissauer's Paralysis: See Dementia Paralytica
Tract: See Spinal Cord
List, C. F.: Sweat secretion in man; spinal reflex sweating, *501
Lobectomy: See Brain, surgery
Lobotomy: See Brain, surgery
Locomotion: See also Movements
movements in decerebrate cat, 195

Longitudinal Sinus, effect of variations in subarachnoid pressure on venous pressure in superior longitudinal sinus and in torcular of dog, 90
Louping Ill: See Encephalomyelitis
Luhan, J. A.: Homonymous hemianopsia; report of 2 unusual cases, 413
Lungs: See also Respiration; etc.
blood supply; cerebral air embolism, 410
Lymphocytes in Meningitis: See Choriomeningitis

McCouch, G. P.: Spinal shock, 298
McGill University, department of psychiatry, 86
Maclay, W. S.: Neurotic disabilities in total war; rehabilitation of patients with neuroses, 580
Malaria, Therapeutic: See Dementia Paralytica; etc.
Malingering and hysteria in nurses, 207
Malnutrition: See Vitamins; etc.
Man, Primitive: See Indians, American
Mania: See Insanity
Matthews, R. A.: Clinical observations on patients with behavior disorders who show abnormal electroencephalograms, 206
Maze, effect of glutamic acid and other amino acids on maze learning in white rat, *446
Medical Jurisprudence: See Jurisprudence, Medical
Medicine, Military: See Military Medicine
Psychosomatic: See Mind
Medin-Heine's Disease: See Poliomyelitis
Medulla Oblongata, abscess of; report of case, *282
aneurysm of vertebral artery; report of case in which aneurysm simulated tumor of posterior fossa, *271
Melancholia: See Insanity, manic-depressive
Involutional: See Mental Diseases
Meninges: See also Arachnoid
hemorrhage; cerebellar extradural hematoma, 94
hemorrhage; fatal intracranial venous hematoma following ventricular drainage, 94
hemorrhage; rupture of aneurysm of circle of Willis; relationship between intraocular and intracranial hemorrhage, 488
tuberculosis; chronic tuberculous cerebrospinal leptomeningitis, 198
tuberculosis; hemiplegia in tuberculous meningitis, 196
Meningitis: See also Choriomeningitis
cerebrospinal fever treated by chemotherapy, 291
meningococcic, treated with sulfathiazole, 198
pneumococcic; recovery after sulfapyridine and serum therapy, 197
response of Pfeiffer's bacillus meningitis to sulfapyridine, 196
Serosa Circumscripta Spinalis: See Arachnoid, inflammation
Tuberculous: See Meninges, tuberculosis
Meningococci: See under Meningitis
Meningoencephalitis: See Encephalitis; Meningitis
Menopause, specific treatment of psychosis due to estrogen deficiency, *462
Mental Deficiency: See Feeblemindedness
Mental Diseases: See also Children; Dementia Paralytica; Dementia Praecox; Feeblemindedness; Insanity; Neuroses and Psychoneuroses; Personality; Psychiatry; etc.
androgen therapy for involutional melancholia, *457
bilateral prefrontal lobotomy, 576
cerebral arteriovenous oxygen difference; mental deficiency, *73
clinical observations on patients with behavior disorders who show abnormal electroencephalograms, 206
convulsive shock therapy in elderly patients, 411
electric shock therapy in psychoses, 491
electroencephalogram as diagnostic aid, 206
electrofit in treatment of, 411
evaluation of complaints after head injury, 409
evaluation of effects of intravenous insulin technic in treatment, 200
experiences in treatment of depressive states by electrically induced convulsions, 292
extramural shock therapy, 200
fatal circulatory failure caused by electric shock therapy, *557
fatalities associated with electric shock treatment of psychoses; report of 2 cases, with autopsy observations in 1 of them, *397
follow-up studies of series of patients treated by electrically induced convulsions and by metrazol convulsions, 411
Mental Diseases—Continued
further statistics on electric shock therapy, 204
prefrontal lobotomy in chronic psychoses, 200
prefrontal lobotomy in treatment, 578
prefrontal lobotomy in treatment; surgical technic, 579
regular 40 to 50 day cycle of psychotic behavior in 14 year old boy, *478
role of cortical respiratory center in production of respiratory distress during electric shock therapy, 205
specific treatment of psychosis due to estrogen deficiency, *462
subconvulsive electric shock treatment of psychoses, 199
treatment of psychoses with long protracted insulin coma, 199
use of refrigeration therapy with report of 16 cases, 290
use of strychnine in curare-aided metrazol treatment of psychoses, 200
Mental Tests: See also Personality
comparison of schizophrenia and manic-depressive disorders with reference to emotional maturity, 92
delirium; electroencephalographic data, *356
physical, psychiatric and psychometric studies of postencephalitic parkinsonism, 91
prognosis in schizophrenic-like psychoses in children, 407
significance of psychologic research in schizophrenia, 407
studies of B vitamins in human subjects; mental changes in experimental deficiency, 89
Merritt, H. H., appointment to Montefiore Hospital, 579
Mesencephalon: See Brain
Metabolism: See under specific headings, as Brain; etc.
Metrazol, Therapy: See Dementia Praecox; Insanity; Mental Diseases; Neuroses and Psychoneuroses; etc.
Meynert Commissure: See Optic Chiasm
Microcephaly, cerebral arteriovenous oxygen difference; mental deficiency, *73
Micropsia: See Vision
Migraine, effect of benzedrine [amphetamine] sulfate on, 289
effect of potassium thiocyanate on occurrence of, 289
personality of patients with, 408
Military Medicine: See also Aviation and Aviators; Neuroses and Psychoneuroses; Recruits; Soldiers and Veterans; etc.
care of head injuries on large scale, 296
cryptic nostalgia, 92
individual issues in postmilitary psychotherapy, 580
neuropsychiatric program for replacement training center, 409
psychiatric problems in military service, 493
Military Surgery: See Surgery, military
Mind, Diseases: See Dementia Praecox; Insanity; Mental Diseases; etc.
fundamental concepts of psychosomatic research; psychogenesis; conversion; specificity, 208
Mongolism, cerebral arteriovenous oxygen difference; mental deficiency, *73
Montefiore Hospital, appointment of H. H. Merritt to, 579
Morons: See Feeblemindedness
Morphine, effects in experimental shock due to hemorrhage, 576
Motion Pictures, analysis of convulsive movements by slow motion pictures, 298
Motoneurons: See Neurons
Movements: See also Locomotion; Muscles
analysis of convulsive movements by slow motion pictures, 298
Disorders: See Parkinsonism; etc.
dystonia; clinical classification, *319
dystonia; historical review; analysis of dystonic symptoms and physiologic mechanisms involved, *305
suppression of motor response in man, *528
Muscles, Atrophy: See Atrophy, muscular
cholinesterase and behavior problem in Amblystoma, 406
effect of prostigmine and acetylcholine on denervated muscle, 406

Muscles—Continued
electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
electromyography as method for determination of level of lesions in spinal cord, *415
factors affecting recovery of motor function after nerve lesions, 97
innervation and function of thenar muscles, 98
innervation and "tonus" of striated muscle in man, 286
neurophysiology of Parkinson tremor, 195
Paralysis: See Paralysis
pronator reflex, *132
scalenus anticus syndrome; types; their characterization, diagnosis and treatment, *432
site of origin of fasciculations in voluntary muscle, *264
specific excitability of end plate region in normal and denervated muscle, 287
studies of neuromuscular disorders; myogram, blood cholinesterase and effects of prostigmine in myasthenia gravis and progressive muscular atrophy, 490
synaptic potentials and transmission in sympathetic ganglion, 91
Myasthenia Gravis, diagnostic tests with prostigmine and quinine, 412
studies of neuromuscular disorders; myogram, blood cholinesterase and effects of prostigmine in myasthenia gravis and progressive muscular atrophy, 490
Myelin: See Brain; Nerves; Pyramidal Tract
Myelopathy: See Spinal Cord
Myerson, A.: Constitutional anhedonia and social neurosis, 497
Tap and thrust responses in Parkinson's disease, *480
Myogram: See Muscles

Narcoanalysis: See Anesthesia
Narcolepsy: See under Sleep
Narcosis: See Anesthesia
Naval Medicine: See Aviation and Aviators; Military Medicine; Recruits; etc.
Neostigmine, diagnostic tests for myasthenia gravis with prostigmine and quinine, 412
effect of prostigmine and acetylcholine on denervated muscle, 406
Nerves: See also Nervous System; Neuralgia; Neuritis; Paralysis
acoustic; tumor within petrous bone; operative removal, *268
anatomicoclinical report of case of carbon monoxide poisoning, with survival for 49 years; correlation of evolution of extrapyramidal symptoms and structural organization of motor pathways of forebrain, 494
Cells: See Neurons
cholinesterase and behavior problem in Amblystoma, 406
cranial; effect of bone dysplasia on cranial nerves in vitamin A-deficient animals, 90
cranial; experimental study on origin of sensory neurons and sheath cells of ninth and tenth cranial nerves in Amblystoma punctatum, 406
development of human mesencephalic trigeminal root and related neurons, 87
electromyography as method for determination of level of lesions in spinal cord, *415
factors affecting recovery of motor function after nerve lesions, 97
factors affecting recovery of sensory function after nerve lesions, 98
independent differentiation of sensory areas of avian inner ear, 89
motor; specific excitability of end plate region in normal and denervated muscle, 287
olfactory, age incidence of atrophy in man; contribution to study of ageing, 192
optic, indirect injuries of, 489
optic; number of myelinated and unmyelinated fibers in optic nerve of vertebrates, 87
optic; numerical relation between ganglion cells of retina and fibers in optic nerve of dog, 87
peripheral, chemical inhibition of fiber regeneration and neuroma formation in, 288
peripheral; procaine nerve block in investigation of peripheral nerve injuries, 97
peroneal; injury due to crossing legs, *179
Nerves—Continued
roots; albuminocytologic dissociation in spinal fluid with xanthochromia, 97
roots; encephalomyeloradiculitis, 198
roots; Guillain-Barré syndrome; early diagnosis, 288
roots; scalenus anticus syndrome; types; their characterization, diagnosis and treatment, *432
sciatic; electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
sensory; functional results of crossing sensory nerves in rat, 192
site of origin of fasciculations in voluntary muscle, *264
Spinal: See Nerves, roots
transynaptic effect of neonatal axon section on bouton appearance about somatic motor cells, 88
trochlear, in human fetuses, 192
Tumors: See Nervous System
vestibular; discharges from vestibular receptors in cat, 194
Nervous System: See also Brain; Cerebellum; Nerves; Neurons; Reflex; Spinal Cord; etc.
Blocking: See Anesthesia
central nervous system in tetanus, 488
Diseases: See also Epilepsy; Mental Diseases; Neuritis; Neuroses and Psychoneuroses; etc.
diseases; torulosis of central nervous system, 578
effect of sectioning various autonomic nerves on rate of emptying of biliary tract in cat, 194
eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452
incidence of metastases to, *423
protective barriers of central nervous system; experimental study with trypan red, *54
removal of acetylcholine by cholinesterase injections and effect thereof on nerve impulse transmission, 487
Surgery: See Brain, surgery; etc.
synthesis of acetylcholine in sympathetic ganglia and cholinergic nerves, 90
Syphilis: See Neurosyphilis
treatment of shock by direct action of vegetative nervous centers, 291
Tumors: See Neuroma; etc.
use of furmethide in testing sweat secretion in man, *568
Nervousness: See Neuroses and Psychoneuroses
Neuritis, neuritides accompanying syphilitic aortitis, 99
polyneuritis following therapy with sulfonamide compound, 99
Sciatic: See Sciatica
Neurohypophysis: See Pituitary Body
Neurology: See Nerves; Nervous System; Neuropsychiatry; Neuroses and Psychoneuroses; etc.
Neuroma, chemical inhibition of fiber regeneration and neuroma formation in peripheral nerves, 288
Neurons, development of human mesencephalic trigeminal root and related neurons, 87
early development of motor cells and columns in spinal cord of sheep, 88
experimental study on origin of sensory neurons and sheath cells of ninth and tenth cranial nerves in Amblystoma punctatum, 406
human pyramidal tract; effect of paralysis produced by cerebral tumors on axons of pyramids, *213
lipofuscin distribution in basal ganglia, 192
numerical relation between ganglion cells of retina and fibers in optic nerve of dog, 87
transynaptic effect of neonatal axon section on bouton appearance about somatic motor cells, 88
Neuropsychiatry: See also Psychiatry; War; etc.
in war, 493
neuropsychiatric program for replacement training center, 409
Neuroses and Psychoneuroses: See also Mental Diseases; Nervous System, diseases; etc.
contitutional anhedonia and social neurosis, 497
neurotic disabilities in total war; rehabilitation of patients with neuroses, 580
physical treatment of acute war neuroses, 291
psychodynamic study of group of patients suffering from arterial hypertension, 100
Neurosurgery: See Brain, surgery

Neurosyphilis: See also Dementia Paralytica
syphilis of central nervous system, 93
treatment of cerebrospinal syphilis, 292, 293
Neurotropism: See Encephalitis
Neustaedter, M.: Incidence of metastases to nervous system, *423
Newbill, H. P.: Racial and sexual incidence of primary intracranial tumors; statistical study of 133 cases verified by autopsy, *564
Newborn Infants: See Infants, newborn
Nicotine, experimental catalepsy produced by, 196
Night Blindness, degeneration and repair of rat retina in avitaminosis A, 575
Nostalgia: See Homesickness
Novocaine [Procaine Hydrochloride]: See under Anesthesia
Nucleus Pulposus: See Spine, intervertebral disk
Nurses and Nursing; hysteria and malingering in nurses, 207
Nutrition: See Vitamins
Nystagmus: See Cerebellum; Ear, internal

Obituaries:

Halloran, Roy Dennis, 190
Sachs, Bernard, 481

Obsessions: See Neuroses and Psychoneuroses
Old Age, cerebral cortex of man with senile dementia believed to be 107 years old, *78
convulsive shock therapy in elderly patients, 411
Olfactory Bulb: See Nerves, olfactory
Oligodendroglioma, oligodendrogliomatosis of cerebrospinal pathway, 407
Oligophrenia: See Feeblemindedness
Olsen, A.: Acute ascending paralysis; Landry's paralysis, 105
Ophthalmoplegia: See Eyes, paralysis
Optic Chiasm, micropsia and teleopsia limited to temporal fields of vision, 410
optochiasmic arachnoiditis, 410
Optic Disk: See Nerves, optic
Optic Pathway: See also Brain; Nerves, optic; Optic Chiasm; Thalamus
structural changes in external geniculate body of rat following removal of eyes, 575
Optic Thalamus: See Thalamus
Osborne, R. L.: Eosinophilic granuloma of bone presenting neurologic signs and symptoms; report of case, *452
Simple automatic pneumoencephalograph, *405
Osteochondroma arising from base of skull, 95
Oxygen: See also Respiration
cerebral arteriovenous oxygen difference; mental deficiency, *73
deficiency; acetylcholine level of rat cerebral cortex under conditions of anoxia and hypoglycemia, 487
deficiency; cerebral metabolism in hypoxia, *472
delirium; reversibility of electroencephalogram with experimental procedures, *378
effect of serum on survival time of brain tissue and revival of cerebral oxidation, *176
in Blood: See under Blood
simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134

Pain: See also Sensation
threshold in man, 285
Palsy: See Paralysis
Paralysis: See also Extremities, paralysis; Eyes, paralysis; Hemiplegia; Larynx, paralysis; Poliomyelitis
acute ascending: Landry's paralysis, 105
agitans; tap and thrust responses in Parkinson's disease, *480
agitans, vitamin B therapy in, 201
Bell's: See Paralysis, facial
facial; congenital paralysis of lateral rotators of eyes with paralysis of muscles of face, 578
facial; occurrence of peripheral facial paralysis in hypertensive vascular disease, 288
Familial Periodic: See Extremities, paralysis
General: See Dementia Paralytica
human pyramidal tract; effect of paralysis produced by cerebral tumors on axons of pyramids, *213
Infantile: See Poliomyelitis
Landry's: See Paralysis, acute ascending
Laryngeal: See Larynx, paralysis
Paralysis—Continued
nature of paresis following lateral corticospinal section in monkeys, 487
of nerve induced by direct pressure and by tourniquet, *1
Periodic: See Extremities, paralysis
Paraplegia: See Extremities, paralysis
Paresis: See Dementia Paralytica
Parietal Lobe: See Brain
Parkinsonism: See also Encephalitis; Paralysis, agitans
cerebral and spinal operations in case of severe postencephalitic tremors, 108
neurophysiology of Parkinson tremor, 195
Perabrodil: See under Spine
Perception: See also Sensation; etc.
disorientation and associated Gerstmann syndrome from intracerebral hemorrhage, 93
loss of emotional expression and body scheme, 93
Personality and environmental factors in psychoses, 576
constitutional anhedonia and social neurosis, 497
of patients with migraine, 408
psychodynamic study of group of patients suffering from arterial hypertension, 100
study of personalities of 289 abnormal drinkers, 409
Perspiration: See under Sweat Glands
Petrous Bone: See Temporal Bone
Peyote: See Anhalonium
Phenytoin Sodium: See Epilepsy
Phobias: See Neuroses and Psychoneuroses
Phosphorus and Phosphorus Compounds, acid-soluble phosphorus compounds of cerebral tissue, 89
Pick's Disease: See Brain, atrophy
Pimenta, A. D.: Sweat secretion in man; spinal reflex sweating, *501
Pitressin: See Pituitary Preparations
Pituitary Body: See also Hypothalamus; Sella Turcica
abscess within sella turcica simulating pituitary tumor; surgical cure, 95
developmental control of pars intermedia by brain, 193
Pituitary Preparations, pitressin diagnosis of idiopathic epilepsy, 89
Plastic Surgery, plastic repair of defects of skull, 202
Pneumoencephalography: See under Brain
Poisons and Poisoning: See under names of various substances, as Carbon Monoxide; etc.
Polioencephalitis: See Encephalitis
Polioencephalomyelitis: See Encephalomyelitis
Poliomyelitis: See also Encephalomyelitis
and tonsillectomy, 198
anterior, Kenny versus orthodox treatment of, 491
Kenny treatment of, 411
recent changes in concept of treatment, 289
relationship between benign lymphocytic meningitis and poliomyelitis, 197
Pollock, L. J.: Electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
Polycythemia vera, chorea complicating, 93
Polyneuritis: See Neuritis
Polyradiculitis: See Nerves, roots
Porencephaly: See Brain, cysts
Position: See Posture
Posture, cerebral air embolism, 410
delirium; reversibility of electroencephalogram with experimental procedures, *378
simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Potassium Chloride: See Cataplexy
Thiocyanate: See Migraine
Pressure, paralysis of nerve induced by direct pressure and by tourniquet, *1
injury to peroneal nerve due to crossing legs, *179
Price, J. C.: Biochemical aspects of glutamic acid therapy for epilepsy, *393
Procaine: See Anesthesia
Prostigmine: See Neostigmine
Proteins, in Cerebrospinal Fluid: See under Cerebrospinal Fluid

Psychiatry: See also Insanity; Jurisprudence, Medical; Mental Diseases; Neuropsychiatry; Psychology; Psychotherapy; War; etc.
department at McGill University, 86
in field of aviation medicine, 493
psychiatric induction examinations, 577
psychiatric problems in military service, 493
Psychology: See also Mental Tests; Personality; War; etc.
peyote intoxication, 408
Psychoneuroses: See Neuroses and Psychoneuroses
Psychoses: See Insanity; Mental Diseases; Neuroses and Psychoneuroses; etc.
Psychotherapy, postmilitary, individual issues in, 580
Puberty: See Adolescence
Putnam, T. J.: Physiologic and clinical aspects of electroencephalogram, 581
Pyramidal Tract, human; effect of paralysis produced by cerebral tumors on axons of pyramids, *213
nature of paresis following lateral corticospinal section in monkeys, 487
new pyramidal sign of great frequency, 94

Quinine, diagnostic tests for myasthenia gravis with prostigmine and quinine, 412

Races: See Indians, American; etc.
racial and sexual incidence of primary intracranial tumors; statistical study of 133 cases verified by autopsy, *564
Radiculitis: See Nerves, roots
Recruits: See also Military Medicine
electroencephalographic study of 275 candidates for military service, 577
psychiatric induction examinations, 577
Reflex, conditioned, effect of electrically and chemically induced convulsions on, 285
experimental studies on development of corneal reflex in amphibia; influence of periphery on reflex center, 193
functional development of fetal brain, 285
homolateral reflex exaggeration after brain-stem lesion, 286
new pyramidal sign of great frequency, 94
orbicularis oculi reflex, *121
patellar; knee jerk, *118
pupillary; removal of acetylcholine by cholinesterase injections and effect thereof on nerve impulse transmission, 487
spinal shock, 298
studies in reflexes; history, physiology, synthesis and nomenclature; study I, *113; correction, 414
sweat secretion in man; spinal reflex sweating, *501
tap and thrust responses in Parkinson's disease, *480
tremor and Babinski sign in alcoholic patients; incidence and interpretation, *403
Refrigeration: See Cold
Rehabilitation, neurotic disabilities in total war; rehabilitation of patients with neuroses, 580
Respiration, delirium; reversibility of electroencephalogram with experimental procedures, *378
effects of increased intraventricular pressure on respiration and circulation, *514
functional development of fetal brain, 285
role of cortical respiratory center in production of respiratory distress during electric shock therapy, 205
Retina, blood supply; visible retinal arteriolar spasm associated with multiple sclerosis; preliminary report, *573
degeneration and repair of rat retina in avitaminosis A, 575
effect of 180 degree rotation of retinal field on visuomotor coordination, 406
numerical relation between ganglion cells of retina and fibers in optic nerve of dog, 87
Reznick, S.: Electronarcosis in animals and in man, *232
Riboflavin: See also Vitamins, B
experimental deficiency in man, 193
Ribs, scalenus anticus syndrome; types; their characterization, diagnosis and treatment, *432
Rice, K. K.: Regular 40 to 50 day cycle of psychotic behavior in 14 year old boy, *478
Riese, W.: Cerebral cortex of man with senile dementia believed to be 107 years old, *78
Rivers, T. D.: Prolonged insulin coma in treatment of schizophrenia, *550
Roberts, C. S.: Integration of electroencephalogram; approach to schizophrenia through electroencephalography, 581
Roentgen Rays, Therapy: See under names of organs, regions and diseases
Romano, J.: Delirium; electroencephalographic data, *356
Delirium; reversibility of electroencephalogram with experimental procedures, *378
Simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Rome, H. P.: Prolonged insulin coma in treatment of schizophrenia, *550
Ross, S.: Effect of glutamic acid and other amino acids on maze learning in white rat, *446
Roy, J. E.: Tremor and Babinski sign in alcoholic patients; incidence and interpretation, *403
Rubrospinal Tract: See Extrapyramidal Tract

Sarcoma: See also Cancer; Tumors
incidence of metastases to nervous system, *423
Scaphocephaly: See Cranium, abnormalities
Schiller, M. A.: Electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
Schizophrenia: See Dementia Praecox
Schroeder, H. T.: Androgen therapy for involutional melancholia, *457
Sciatica, problem of primary sciatic neuritis; analysis of 55 cases, 96
Sclerosis, visible retinal arteriolar spasm associated with multiple sclerosis; preliminary report, *573
Scotoma, visible retinal arteriolar spasm associated with multiple sclerosis, *573
Scott, M.: Cerebral and spinal operations in case of severe postencephalitic tremors, 108
Selective Service: See Recruits
Sella Turcica: See also Pituitary Body
abscess within sella turcica simulating pituitary tumor; surgical cure, 95
Senile Plaque: See Sclerosis
Senility: See Old Age
Sensation: See also Nerves, sensory; Pain; etc.
factors affecting recovery of sensory function after nerve lesions, 98
sensory reception in hysterical anesthesia as measured by cold pressor response, *84
Serum Therapy: See Meningitis
Sex, perversion; indecent exposure (sexual exhibitionism); 100 cases, 91
racial and sexual incidence of primary intracranial tumors; statistical study of 133 cases verified by autopsy, *564
Shannon, E. W.: Colloid cyst of third ventricle, *570
Sherman, I. C.: Electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
Shock, action of adrenalin on transmission in sympathetic ganglia, which may play part in shock, 90
effects of morphine in experimental shock due to hemorrhage, 576
Electric: See Dementia Praecox; Electrotherapy; Epilepsy; Mental Diseases; etc.
treatment by direct action of vegetative nervous centers, 281
Silverstein, A.: Familial periodic paralysis, 103
Simeone, F. A.: Scalenus anticus syndrome; types; their characterization, diagnosis and treatment, *432
Sinus, Longitudinal: See Longitudinal Sinus
Skull: See Cranium
Sleep, disorders; diplopia in narcolepsy, 488
disorders; relation of narcolepsy to epilepsies; clinical-electroencephalographic study, *163
Smith, W. A.: Torular granuloma simulating cerebral tumor; report of 2 cases, *426
Snyder, R.: Biochemical studies on patients with schizophrenia; dextrose, oxygen and carbon dioxide contents of arterial and venous blood from cranial cavity, *469
Societies, American Board of Psychiatry and Neurology, Inc., 86, 212, 414
American Branch of International League Against Epilepsy, 579
National Committee for Mental Hygiene, 414

Society Transactions:
Boston Society of Psychiatry and Neurology, 100, 295, 494
Chicago Neurological Society, 202, 413
Illinois Psychiatric Society, 207
Michigan Society of Neurology and Psychiatry, 580
New York Academy of Medicine, Section of Neurology and Psychiatry, and New York Neurological Society, 581
Philadelphia Neurological Society, 103, 298
Philadelphia Psychiatric Society, 204, 493
Sodium Amytal: See Dementia Praecox
Diphenylhydantoinate: See Epilepsy
Soldiers and Veterans: See also Military Medicine; Neuroses and Psychoneuroses; etc.
individual issues in postmilitary psychotherapy, 580
Somnolence: See Sleep
Sonenthal, I. R.: Hysteria and malingering in nurses, 207
Spasm: See Convulsions; Epilepsy; etc.
Sphenoid Bone, osteochondromas arising from base of skull, 95
Spinal Cord: See also Meninges; Nervous System; Pyramidal Tract; etc.
abscess within; review of literature and report of 3 cases, *533
aneurysm of vertebral artery; report of case in which aneurysm simulated tumor of posterior fossa, *271
early development of motor cells and columns in spinal cord of sheep, 88
electromyography as method for determination of level of lesions in, *415
epidermoid tumor of, 287
epileptiform attacks produced by sudden cooling of frog spinal cord, 286
injuries; present concept and status of medullary contusion, 288
nature of paresis following lateral corticospinal section in monkeys, 487
spinal shock, 298
surgery; cerebral and spinal operations in case of severe postencephalitic tremors, 108
sweat secretion in man; spinal reflex sweating, *501
transynaptic effect of neonatal axon section on bouton appearance about somatic motor cells, 88
Spinal Fluid: See Cerebrospinal Fluid
Spine, intervertebral disk; epidural contrast investigation (with perabrodil) of lumbosacral canal in prolapse of disk, 294
intervertebral disk; herniation of nucleus pulposus as complication of pre-existing low back instability, 489
intervertebral disks, protruded, 489
spinal injuries in shock and epileptic convulsions, 293
Spinothalamic Tract: See Spinal Cord
Status Epilepticus: See under Epilepsy
Stevens, C. D.: Simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Stewart, W. B.: Spinal shock, 298
Stilbestrol: See Estrogens
Stone, W. E.: Cerebral metabolism in hypoxia, *472
Strait, L.: Protective barriers of central nervous system; experimental study with trypan red, *54
Strecker, E. A.: Neuropsychiatry in war, 493
Strychnine, use in curare-aided metrazol treatment of psychoses, 200
Subarachnoid Space: See Meninges
Subdural Spaces: See Meninges
Sugar in Blood: See Blood sugar
Sulfathiazole: See Meningitis; Sulfonamides
Sulfonamides, dysmorphopsia during course of sulfanilamide therapy, 489
polyneuritis following therapy with sulfonamide compound, 99
Therapy: See Gonorrhea; Meningitis; etc.
Sullivan, J. D.: Sensory reception in hysterical anesthesia as measured by cold pressor response, *84
Suprarenal Preparations: See Adrenal Preparations
Surgery: See also Apparatus; Instruments; and under organs and regions, as Brain, surgery; Eyes, surgery; Spinal Cord, surgery; etc.
Surgery—Continued
military; neurosurgical experience in Egypt and Libya, 295
Plastic: See Plastic Surgery
Swank, R. L.: Scalenus anticus syndrome; types; their characterization, diagnosis and treatment, *432
Swanson, H. S.: Torular granuloma simulating cerebral tumor; report of 2 cases, *426
Sweat Glands, sweat secretion in man; spinal reflex sweating, *501
use of furmethide in testing sweat secretion in man, *568
Sympathectomy: See Blood pressure, high
Syphilis: See Neurosyphilis; and under names of organs and regions, as Aorta; etc.

Telencephalon: See under Brain
Teleopsia: See Vision
Temporal Bone, tumor of acoustic nerve within petrous bone; operative removal, *268
Testosterone: See Androgens
Tetanus, central nervous system in, 488
paralysis of left recurrent laryngeal nerve following subcutaneous administration of antitetanic serum, 98
Thalamus, effects on electroencephalogram of chronic lesions of basal ganglia, thalamus and hypothalamus of monkeys, 487
Thale, T.: Acetylcholine treatment of schizophrenia, *171
Thrombosis: See also Embolism
of common carotid artery, 197
Tigay, E. L.: Electrodiagnosis by means of progressive currents of long duration; studies on cats with experimentally produced section of sciatic nerves, *147
Tissenbaum, M. J.: Acetylcholine treatment of schizophrenia, *171
Tocopherol: See Vitamins, E
Tonsillectomy and poliomyelitis, 198
Torcular Herophili: See Dura Mater
Torulosis of central nervous system, 578
torular granuloma simulating cerebral tumor; report of 2 cases, *426
Touch, periodicity in development of threshold of tactile stimulation in Amblystoma, 286
Tourniquet: See Hemostasis
Toxicomania: See Drugs, addiction
Trauma: See Brain, injuries; Head, injuries; Nerves, optic; Spine, injuries; etc.
Tremor: See also Paralysis agitans; Parkinsonism and Babinski sign in alcoholic patients; incidence and interpretation, *403
cerebral and spinal operations in case of severe postencephalitic tremors, 108
Trypan Red, protective barriers of central nervous system; experimental study with trypan red, *54
Tuber Cinereum: See Hypothalamus
Tuberculosis: See under names of organs, regions and diseases, as Meninges; etc.
Tuberculum Sellae: See Hypothalamus
Tumors: See also Angioma; Granuloma; Neuroma; Oligodendroglioma; Osteochondroma; Sarcoma; etc.; and under names of organs and regions, as Brain; Cranium; Nerves, acoustic; Pituitary Body; Spinal Cord; etc.
epidermoid, of spinal cord, 287
Turner, W. J.: Integration of electroencephalogram; approach to schizophrenia through electroencephalography, 581
Tyler, D. B.: Electronarcosis in animals and in man, *232

Unger, A. A.: Androgen therapy for involutional melancholia, *457
Universities, manic-depressive psychoses among college students, 576

van Harreveld, A.: Electronarcosis in animals and in man, *232
Vasomotor System: See also Arteries; Nervous System
sensory reception in hysterical anesthesia as measured by cold pressor response, *84
Veins, Pressure in: See Blood pressure
Vertebrae: See Spine
Vestibular Apparatus: See Ear
Veterans: See Soldiers and Veterans

Vision, defective; disintegration and restoration of optic recognition in visual agnosia; analysis of case, *243
defective; dysmorphopsia during course of sulfanilamide therapy, 489
effect of 180 degree rotation of retinal field on visuomotor coordination, 406
micropsia and teleopsia limited to temporal fields of, 410
new answer to question of macular sparing, 575
Vitamins: See also Riboflavin
A; degeneration and repair of rat retina in avitaminosis A, 575
A; effect of bone dysplasia on cranial nerves in vitamin A-deficient animals, 90
B: See also Riboflavin
B; studies in human subjects; mental changes in experimental deficiency, 89
B therapy in paralysis agitans, 201
B_2: See Riboflavin
E; neurologic and endocrine aspects of atrophic arthritis (deformans), 491
Vocal Cords, Paralysis: See Larynx, paralysis
Vocation, neurotic disabilities in total war; rehabilitation of patients with neuroses, 580
Voris, H. C.: Plastic repair of defects of skull, 202

Waelsch, H.: Biochemical aspects of glutamic acid therapy for epilepsy, *393
Walker, A. E.: Diagnostic value of electroencephalography, 203
War: See also Aviation and Aviators; Military Medicine; Soldiers and Veterans; etc.
neuropsychiatry in, 493
neurotic disabilities in total war; rehabilitation of patients with neuroses, 580
Wartenberg, R.: Studies in reflexes; history, physiology, synthesis and nomenclature; study I, *113; correction, 414
Watts, J. W.: Abscess of medulla oblongata; report of case, *282
Webb, J. P.: Simple method of determining frequency spectrums in electroencephalogram; observations on effects of physiologic variations in dextrose, oxygen, posture and acid-base balance on normal electroencephalogram, *134
Webster, J. E.: Cerebral metabolism in hypoxia, *472
Weickhardt, G. D.: Abscess of medulla oblongata; report of case, *282
Whitehorn, J. C.: Individual issues in postmilitary psychotherapy, 580
Wiersma, C. A. G.: Electronarcosis in animals and in man, *232
Willis, Circle of: See Aneurysm
Wortis, J.: Effect of serum on survival time of brain tissue and revival of cerebral oxidation, *176
Wright, T., Jr.: Further statistics on electric shock therapy, 204

Xanthochromia; albuminocytologic dissociation in spinal fluid with xanthochromia, 97

Yakovlev, P. I.: Anatomicoclinical report of case of carbon monoxide poisoning, with survival for 49 years; correlation of evolution of extrapyramidal symptoms and structural organization of motor pathways of forebrain, 494
Roy Dennis Halloran, 190
Yaskin, H. E.: Aneurysm of vertebral artery; report of case in which aneurysm simulated tumor of posterior fossa, *271

Zfass, I. S.: Cerebral cortex of man with senile dementia believed to be 107 years old, *78
Ziegler, L. H.: Bilateral prefrontal lobotomy; perspective and recent survey of results, 202
Zimmerman, F. T.: Effect of glutamic acid and other amino acids on maze learning in white rat, *446